**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

| | | |
|---|---|---|
| PFIZER INC,<br>PFIZER IRELAND PHARMACEUTICALS,<br>WARNER-LAMBERT COMPANY,<br>WARNER-LAMBERT COMPANY, LLC<br>and<br>WARNER-LAMBERT EXPORT LTD.,<br><br>Plaintiffs,<br><br>v.<br><br>TEVA PHARMACEUTICALS USA, INC.,<br><br>Defendant. | ) | Civil Action No. 08-___ |

**COMPLAINT**

Pfizer Inc, Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Limited, (collectively referred to as "Pfizer"), by their attorneys, for their complaint against Teva Pharmaceuticals USA, Inc. ("Teva"), allege as follows:

1. This is an action by Pfizer against Teva for infringement of United States Letters Patent No. 5,273,995 ("the '995 patent"). A copy of the '995 patent is attached hereto as Exhibit A.

2. On December 28, 1993, the United States Patent and Trademark Office issued the '995 patent, entitled "[R-(R*R*)]-2-(4-Fluorophenyl)-β, δ-Dihydroxy-5-(1-Methylethyl-3-Phenyl-4-[(Phenylamino) Carbonyl]-1H-Pyrrole-1-Heptanoic Acid, Its Lactone Form And Salts Thereof", on an application filed by Bruce D. Roth and assigned to Warner-Lambert Company.

## PARTIES, JURISDICTION AND VENUE

3. Pfizer Inc is a corporation organized and existing under the laws of the State of Delaware and has a place of business at 235 East 42nd Street, New York, New York 10017.

4. Warner-Lambert Company is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York 10017. Warner-Lambert Company has been the owner of record of the '995 patent since its issuance.

5. Warner-Lambert Company became a wholly owned subsidiary of Pfizer Inc effective June 19, 2000.

6. Warner-Lambert Company was converted into Warner-Lambert Company, LLC, a Delaware limited liability company by certificate dated December 31, 2002. Warner-Lambert Company, LLC has offices located at 235 East 42nd Street, New York, New York 10017.

7. Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Pfizer Ireland Pharmaceuticals is a wholly owned, indirect subsidiary of Pfizer Inc.

8. Warner-Lambert Export, Ltd. is a corporation formerly organized under the laws of Ireland with a registered office located at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland.

9. The exclusive licensee of the '995 patent is Pfizer Ireland Pharmaceuticals, formerly Warner-Lambert Export, Ltd.

10. Pfizer holds an approved New Drug Application for an atorvastatin calcium formulation which it sells under the registered name Lipitor®.

11. The '995 patent is identified pursuant to 21 U.S.C. §355 (b)(1) by the United States Food and Drug Administration ("FDA") as covering Pfizer's Lipitor® product.

12. Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, and has a principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania 19454.

13. This action arises under the Patent Laws of the United States, Title 35, United States Code. This Court has subject matter jurisdiction over this action pursuant to the provisions of Title 28, United States Code, Sections 1331 and 1338.

14. Teva is subject to personal jurisdiction in this District.

15. Venue is proper in this District pursuant to the provisions of Title 28, United States Code, Sections 1391 (c), (d) and 1400 (b).

16. An amended final judgment declaring claim 6 of the '995 patent invalid pursuant to the provisions of 35 U.S.C. § 112, ¶ 4 has been entered by the United States District Court for the District of Delaware in Civil Action No. 03-209-JJF, by Orders of the Court dated November 7, 2006 and November 30, 2006 (D.I. 338 and 344). A copy of the final judgment, as amended, is attached as Exhibit B. No relief is sought herein pursuant to claim 6 of the '995 patent.

17. Pfizer received a letter dated April 24, 2007 from Teva (the "April 24, 2007 letter") which notified Pfizer that Teva had filed an Abbreviated New Drug Application (ANDA No. 78-773), seeking approval from FDA to engage in the commercial manufacture, use, and sale of a product containing atorvastatin calcium as the active ingredient prior to the expiration of the '995 patent.

18. The April 24, 2007 letter stated that ANDA No. 78-773 was limited to 80 milligram atorvastatin calcium tablets.

19. On June 7, 2007 Pfizer brought suit against Teva in the United States District Court for the District of Delaware, designated Civil Action No. 07-360 (JJF), alleging infringement of the '995 patent under 35 U.S.C. § 271(e)(2) by filing Teva's ANDA seeking approval from the FDA to engage in the commercial manufacture, use, or sale of a product containing atorvastatin calcium as an active ingredient prior to the expiration of the '995 patent.

20. As of this date, Civil Action No. 07-360 (JJF) remains pending.

**FIRST CLAIM FOR RELIEF;**
**INFRINGEMENT OF THE '995 PATENT**

21. Pfizer realleges paragraphs 1 through 20 above as if fully set forth herein.

22. Pfizer has received a letter dated March 12, 2008 from Teva (the "March 12, 2008 letter") which notified Pfizer that Teva had filed an amendment to ANDA No. 78-773 ("Amended ANDA No. 78-773"), seeking further approval from FDA to engage in the commercial manufacture, use, and sale of a product containing atorvastatin calcium as the active ingredient prior to the expiration of the '995 patent. The March 12, 2008 Letter states that the further FDA approval sought by Teva in Amended ANDA No. 78-773 is for 10, 20, and 40 milligram atorvastatin calcium tablets. A copy of the March 12, 2008 letter is attached hereto as Exhibit C.

23. The expiration date for the '995 patent is December 28, 2010.

24. Lipitor® was granted a further period of exclusivity under section 505 of the Food, Drug and Cosmetic Act to June 28, 2011.

25. Teva has infringed the '995 patent under 35 U.S.C. 271 (e)(2) by filing Amended ANDA No. 78-773 seeking approval from the FDA to engage in the commercial manufacture,

use, or sale of a product containing atorvastatin calcium as an active ingredient prior to the expiration of the '995 patent.

26. Pfizer will be irreparably harmed if Ranbaxy is not enjoined from infringing the '995 patent.

**WHEREFORE,** Pfizer requests the following relief:

A. A judgment providing that pursuant to 35 U.S.C. §271 (e) (4) (A), the effective date of any FDA approval for Teva's Amended ANDA No. 78-773 be no earlier than June 28, 2011, the date of expiration of the '995 Patent including the period of exclusivity granted to Lipitor under section 505 of the Food, Drug and Cosmetic Act;

B. A judgment pursuant to 35 U.S.C. §271 (e) (4) (B) permanently enjoining Teva Pharmaceuticals USA, Inc., each of its officers, agents, servants, employees and attorneys, and those persons in active concert or participation with it or any of them, from making, using, selling, offering to sell, or importing the atorvastatin calcium product described in Teva's Amended ANDA 78-773 until June 28, 2011, the expiration date of the '995 patent including the period of exclusivity granted to Lipitor under section 505 of the Food, Drug and Cosmetic Act;

C. Attorneys' fees in this action under 35 U.S.C. §285;

D. Costs and expenses in this action; and

E. Such further and other relief as this Court may deem just and proper.

RESPECTFULLY SUBMITTED,

*/s/ Rudolf E. Hutz*

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Dated: April 25, 2008

US005273995A

# United States Patent [19]

Roth

[11] Patent Number: 5,273,995

[45] Date of Patent: Dec. 28, 1993

[54] **[R-(R*R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF**

[75] Inventor: **Bruce D. Roth**, Ann Arbor, Mich.

[73] Assignee: **Warner-Lambert Company**, Morris Plains, N.J.

[21] Appl. No.: **660,976**

[22] Filed: **Feb. 26, 1991**

**Related U.S. Application Data**

[63] Continuation of Ser. No. 384,187, Jul. 21, 1989, abandoned.

[51] **Int. Cl.**[5] ..... **A61K 31/40**; C07D 405/06

[52] **U.S. Cl.** ..... **514/422**; 514/423; 548/517; 548/537

[58] **Field of Search** ..... 514/422, 423; 548/517, 548/537

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,681,893 7/1987 Roth ..... 514/223

OTHER PUBLICATIONS

J. Med. Chem. 1985, 28, 347–358—G. E. Stokker, et al. "3-Hydroxy-3-Methylglutaryl-Coenzyme a Reductase . . . ".

Tetrahedron Letters, vol. 28, No. 13, pp. 1385–1388, 1987 "Synthesis of an HMG-COA Reductase Inhibitor, . . . ".

*Primary Examiner*—Mary C. Lee
*Assistant Examiner*—Jacqueline Haley
*Attorney, Agent, or Firm*—Ronald A. Daignault

[57] **ABSTRACT**

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.

**12 Claims, No Drawings**

# [R-(R*R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF

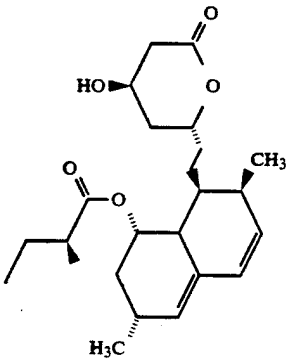
This is a continuation of U.S. application Ser. No. 07/384,187 filed Jul. 21, 1989, abandoned.

## BACKGROUND OF THE INVENTION

Trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamides are among compounds of U.S. Pat. No. 4,681,893 having usefulness as inhibitors of cholesterol biosynthesis. The compounds therein broadly include 4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom.

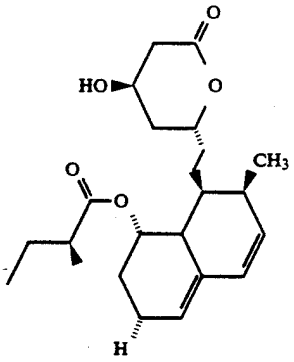
It is now unexpectedly found that the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; that is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, provides surprising inhibition of the biosynthesis of cholesterol.

It is known that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) exists as the 3R-stereoisomer. Additionally, as shown in the study of a series of 5-substituted 3,5-dihydroxypentanoic acids by Stokker et al., in "3-Hydroxy-3-methylglutaryl-Coenzyme A Reductase Inhibitors. 1. Structural Modification of 5-Substituted 3,5-Dihydroxypentanoic acids and Their Lactone Derivatives," *J. Med. Chem.* 1985, 28, 347–358, essentially all of the biological activity resided in the trans diastereomer of (E)-6-[2-(2,4-dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyranone having a positive rotation. Further, the absolute configuration for the β-hydroxy-δ-lactone moiety common to mevinolin of the formula (1a)



1a

and compactin of the formula (1b)



1b

apparently is required for inhibition of HMG-CoA reductase. This is reported by Lynch et al. in "Synthesis of an HMB-CoA Reductase Inhibitor; A diastereoselective Aldol Approach in Tetrahedron Letters, Vol. 28, No. 13, pp. 1385–1388 (1987) as the 4R, 6R configuration.

However, an ordinarily skilled artisan may not predict the unexpected and surprising inhibition of cholesterol biosynthesis of the present invention in view of these disclosures.

## SUMMARY OF THE INVENTION

Accordingly the present invention provides for compounds consisting of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid (compound of formula I), pharmaceutically acceptable salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (the lactone form of the heptanoic acid or compound of formula II).

The present invention also relates to a pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, its pharmaceutically acceptable salts or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide acid; and a pharmaceutically acceptable carrier. Further, the present invention is also a method of treating mammals, including humans, suffering from hypercholesterolemia by administering to such mammal a dosage form of the pharmaceutical composition described above.

## DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutically acceptable salts of the invention are those generally derived by dissolving the free acid or the lactone; preferably the lactone, in aqueous or aqueous alcohol solvent or other suitable solvents with an appropriate base and isolating the salt by evaporating the solution or by reacting the free acid or lactone; preferably the lactone and base in an organic solvent in which the salt separates directly or can be obtained by concentration of the solution.

In practice, use of the salt form amounts to use of the acid or lactone form. Appropriate pharmaceutically acceptable salts within the scope of the invention are

those derived from bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, 1-deoxy-2-(methylamino)-D-glucitol, magnesium hydroxide, zinc hydroxide, aluminum hydroxide, ferrous or ferric hydroxide, ammonium hydroxide or organic amines such as N-methylglucamine, choline, arginine and the like. Preferably, the lithium, calcium, magnesium, aluminum and ferrous or ferric salts are prepared from the sodium or potassium salt by adding the appropriate reagent to a solution of the sodium or potassium salt, i.e., addition of calcium chloride to a solution of the sodium or potassium salt of the compound of the formula I will give the calcium salt thereof.

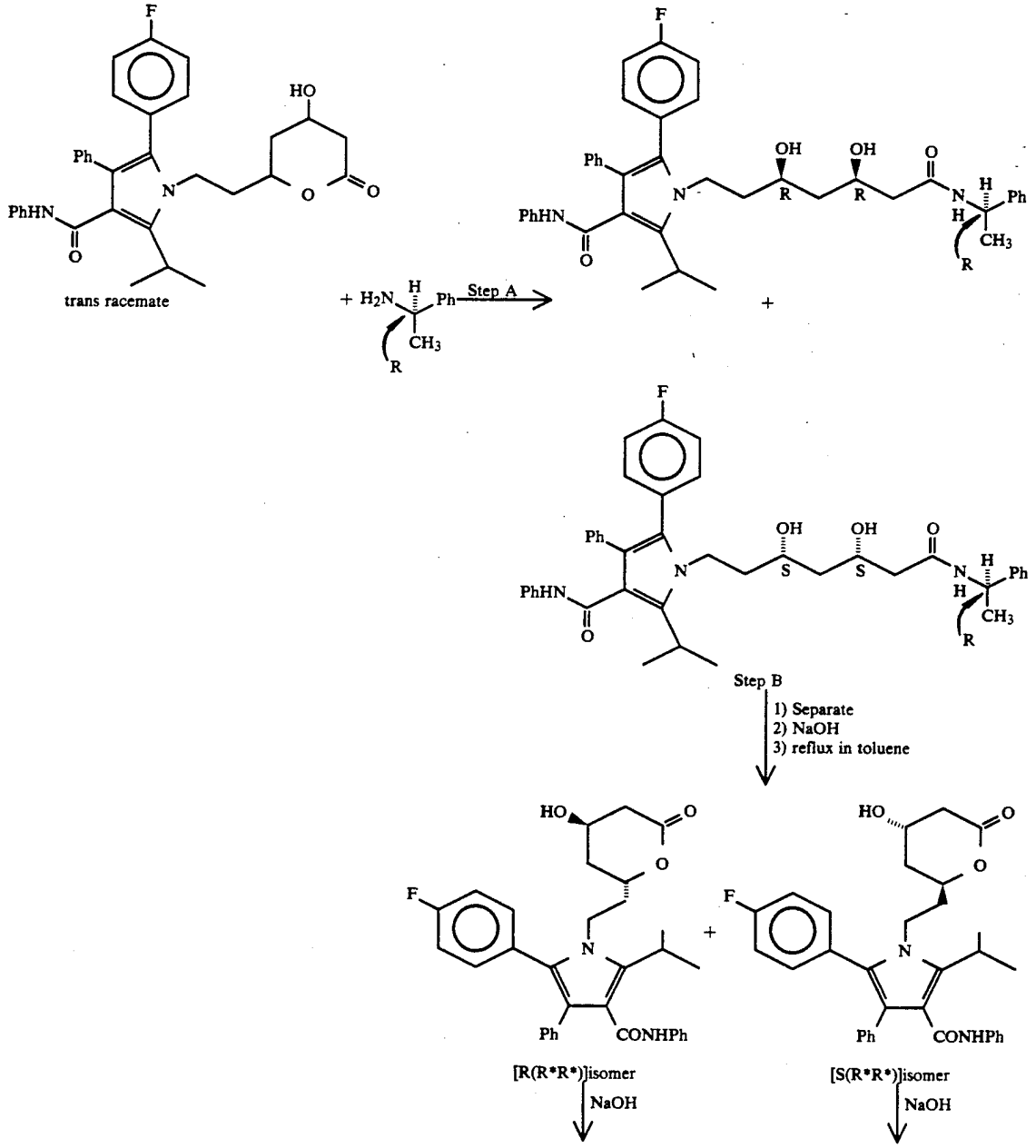
The free acid can be prepared by hydrolysis of the lactone form of formula II or by passing the salt through a cationic exchange resin (H+resin) and evaporating the water.

The most preferred embodiment of the present invention is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt.

Generally, the compounds I and II of the present invention can be prepared by (1) resolving the racemate, that is prepared by the processes described in U.S. Pat. No. 4,681,893 which is incorporated by reference therefor, or (2) synthesizing the desired chiral form beginning from starting materials which are known or readily prepared using processes analogous to those which are known.

Specifically, resolution of the racemate may be accomplished as shown in Scheme I (where Ph is phenyl) as follows:

Scheme 1



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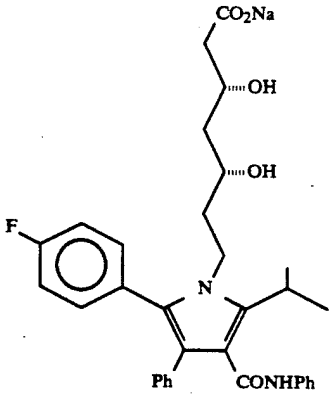
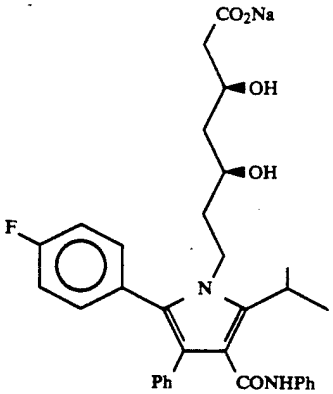
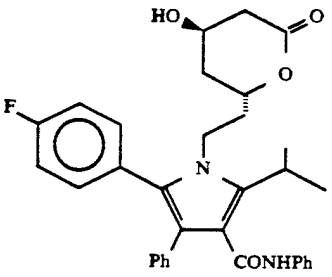
Scheme 1



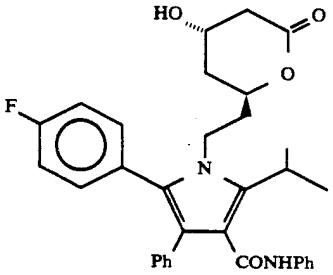

The "trans racemate" of Scheme 1 means a mixture of the following:




[R(R*R*)]isomer

and

-continued

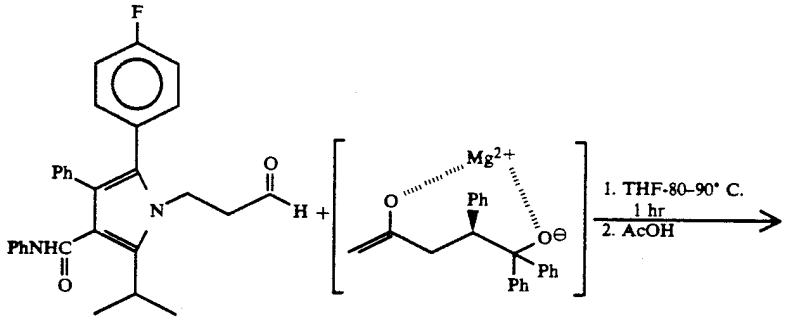


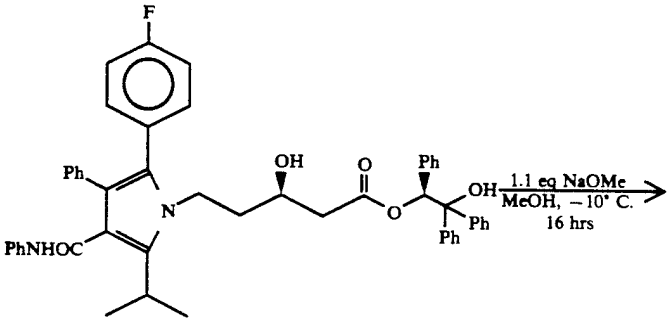

[S(R*R*)]isomer

The conditions of the Step 1 and 2 of Scheme 1 are generally as found in the Examples 6 and 7 hereinafter.

The chiral synthesis is shown in Scheme 2 (where Ph is phenyl) as follows:

Scheme 2




73% (3)

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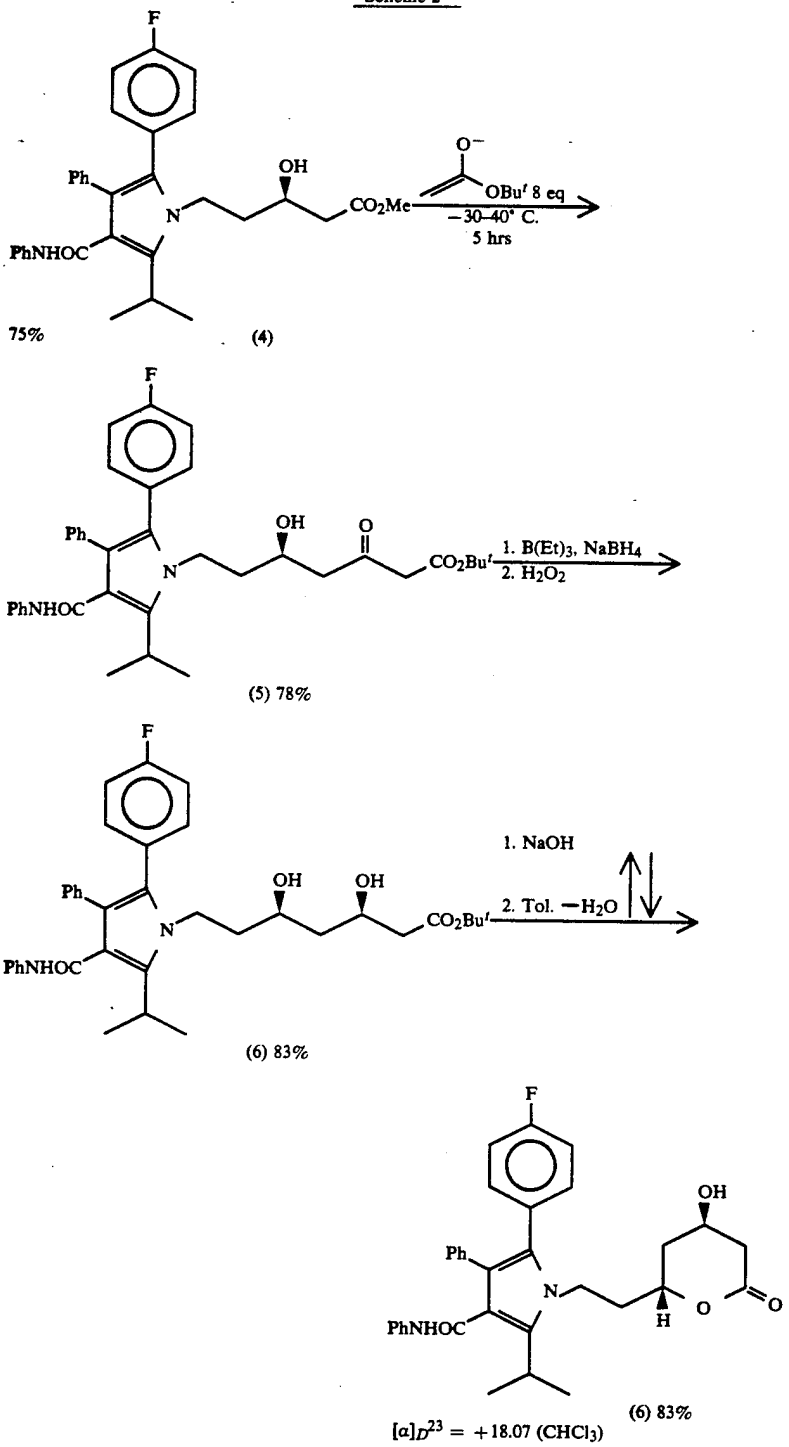
Scheme 2




Generally, conditions for Scheme 2 are as shown in the Examples 1–5 hereinafter.

One of ordinary skill in the art would recognize variations in the Schemes 1 and 2 which are appropriate for the preparation of the compounds of the present invention.

The compounds according to present invention and especially according to the compound of the formula I inhibit the biosynthesis of cholesterol as found in the CSI screen that is disclosed in U.S. Pat. No. 4,681,893 which is now also incorporated by reference therefor. The CSI data of the compound I, its enantiomer the compound II and the racemate of these two compounds are as follows:

| Compound | $IC_{50}$ (micromoles/liter) |
|---|---|
| [R-(R*R*)] isomer | 0.0044 |

-continued

| Compound | $IC_{50}$ (micromoles/liter) |
|---|---|
| [S-(R*R*)] isomer | 0.44 |
| Racemate | 0.045 |

Accordingly, the present invention is the pharmaceutical composition prepared from the compound of the formula I or II or pharmaceutically acceptable salts thereof.

These compositions are prepared as described in U.S. Pat. No. 4,681,893 which is, therefore, again incorporated by reference here.

Likewise, the present invention is a method of use as hypolipidemic or hypocholesterolemic agents. The compounds of the present invention utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 10 to 500 mg per day which for a normal human adult of approximately 70 kg is a dosage of from 0.14 to 7.1 mg/kg of body weight per day. The dosages may be preferably from 0.5 to 1.0 mg/kg per day.

The dosage is preferably administered as a unit dosage form. The unit dosage form for oral or parenteral use may be varied or adjusted from 10 to 500 mg, preferably from 20 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other active therapeutic agents. Determinations of optimum dosages for a particular situation is within the skill of the art.

The compounds of the formula I and II and their pharmaceutically acceptable salts are in general equivalent for the activity of the utility as described herein.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are thus not to be read as limiting the scope of the invention.

## EXAMPLE 1

285 ml 2.2M n-butyl lithium (in Hexane) is added dropwise to 92 ml diisopropylamine in 300 ml THF at 50°–60° C. in a 1000 ml 1 neck flask via dropping funnel and under nitrogen. The well stirred yellow solution is allowed to warm to about −20° C. Then it is cannulated into a suspension of 99 g S(+)-2-acetoxy-1,1,2-triphenylethanol in 500 ml absolute THF, kept in a 2L-3 neck flask at −70° C. When addition is complete, the reaction mixture is allowed to warm to −10° C. over a period of two hours. Meanwhile, a suspension of 0.63 mol $MgBr_2$ is prepared by dropping 564 ml (0.63 mol) of bromine into a suspension of 15.3 g of magnesium (0.63 mol) in 500 ml THF plus in 3 L flask equipped with reflux condenser, and overhead stirrer. When this is completed, the $MgBr_2$ suspension is cooled to −78° C. and the enolate solution (dark brown) is cannulated into the suspension within 30 minutes. Stirring is continued for 60 minutes at −78° C. 150 g 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide in 800 ml THF absolute was added dropwise over 30 minutes; then stirred for 90 minutes at −78° C., then quenched with 200 ml AcOH at −78° C. This is removed to a cool bath, 500 ml of $H_2O$ is added and the mixture concentrated in vacuo at 40°–50° C. 500 ml of 1:1 EtOAc/Heptane is added to the yellowish slurry and filtered. The filtrate is washed extensively with 0.5N HCl, then several times with $H_2O$ and finally with EtOAc/Heptane (3:1) that was cooled with dry ice to −20° C. The light brown crystalline product (Example 1A) is dried in vacuum oven at 40° C. The yield is 194 g.

The product 1A is recrystallized from EtOAc at −10° C. to yield 100 g to yield product 1B and then recrystallized from acetone/pentane to yield 90 g to yield product 1C. The mother liquor is combined from the wash of the crude material and recrystallized from EtOAc/Hexane. 33 g of 1B shows the following: HPLC: 97.4:2.17 of the R,S to S,S isomers. 28.5 g of 1C shows the following: HPLC:95.7:3.7. The combined 1B and 1C is recrystallized from $CHCl_3$ MeOH 10:1; providing a product 1F having a yield of 48.7 g of white crystal.

The mother liquor of the first aqueous wash is crystallized (EtOAc/Heptane) to yield product 1D of 21.4 g; HPLC: 71.56:25.52.

The mother liquor of 1B and 1C is combined and recrystallized from $CHCl_3$/MeOH/Heptane to yield 55.7 g white crystals of product 1G.

1D is recrystallized from $CHCl_3$/MeOH to yield the product 1H.

All mother liquor is combined, concentrated then the residue is dissolved in hot $CHCl_3$/MeOH 10:1; put on a silica gel column; and eluted with EtOAc/Hexane 40:60. The material crystallized out on the column and the silica gel is extracted with $CHCl_3$/MeOH and concentrated. Recrystallization of the residue from $CHCl_3$/Heptane 3:1 yields 33.7 g of product 1I.

The mother liquor of 1I is recrystallized to yield 18.7 g of product 1K.

The mother liquor of 1K is crystallized to yield 6.3 g of product 1L.

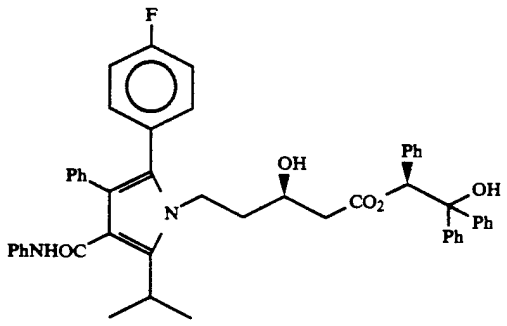
1I, 1K and 1L is combined and recrystallized from $CHCl_3$/Heptane to yield 48 g.

The combined mother liquor of 1I, 1K, and 1L is concentrated to yield 31 g of 1M.

The product 1F provides the following data.

| Anal: 1F m.p. 229–230° C. | |
|---|---|
| Calc. | Found |
| C: 77.84 | 77.14 |
| H: 6.02 | 6.45 |
| N: 3.56 | 3.13 |

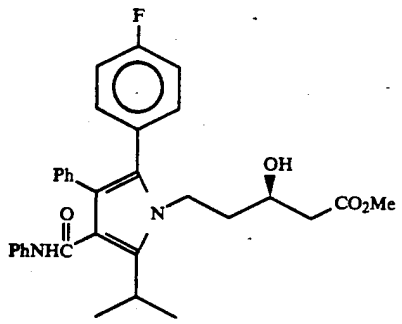
These data are consistent with the formula




## EXAMPLE 2

162 g (0.206M) of the combined products 1F, 1G, 1H and 1L of Example 1 are suspended in 800 ml Methanol/THF (5:3). Cooled to 0° C. and added to 11.7 g

sodium methoxide. The mixture is stirred until everything is dissolved, then put in the freezer overnight. The reaction mixture is allowed to warm to room temperature, quenched with 15 ml HOAc, then concentrated in vacuo at 40° C. to obtain expected product as follows:




This product is added to 500 ml $H_2O$ and extracted twice with EtOAc (300 ml). The combined extracts are washed with saturated $NaHCO_3$, brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated. The residue is chromatographed on silica gel in EtOAc/Heptane (1:4) as eluent to yield 109 g colorless oil which is recrystallized from $Et_2O$/Heptane to yield:

73.9 g first crop; white crystals

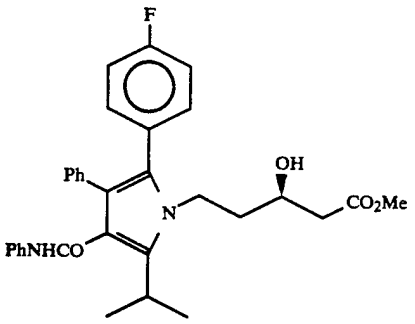
8.2 g second crop; white crystals.

The crystals provide the following data:

m.p. 125°-126° C., $\alpha_D^{20}$=4.23° (1.17M, $CH_3OH$)

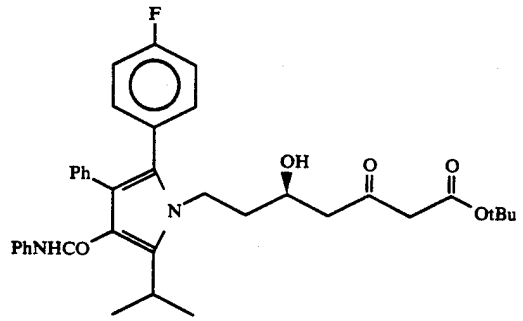
| Calc. | Found |
|---|---|
| C: 72.76 | 72.51 |
| H: 6.30 | 6.23 |
| N: 5.30 | 5.06 |

These data are consistent with the formula




## EXAMPLE 3

77 ml of diisopropylamine is dissolved in 250 ml THF in a 2000 ml three-neck flask equipped with thermometer and dropping funnel. The reaction mixture is kept under nitrogen. The mixture is cooled to −42° C. and added to 200 ml 2.2M of n-butyl lithium (in Hexane) dropwise over 20 minutes and stirred for 20 minutes before adding dropwise 62 ml of t-butylacetate, dissolved in 200 ml THF (over about 30 minutes). This mixture is stirred 30 minutes at −40° C., then 140 ml 2.2M of n-butyl lithium is added over 20 minutes. When addition is complete, 81 g of the product of Example 2 in 500 ml absolute THF is added as quickly as possible without allowing the temperature to rise above −40° C. Stirring is continued for four hours at −70° C. The reaction mixture is then quenched with 69 ml glacial acetic acid and allowed to warm to room temperature. The mixture is concentrated in vacuo and the residue is taken up in EtOAc, washed with water extensively, then saturated $NH_4Cl$, $NaHCO_3$ (saturated), and finally with brine. The organic layer is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The NMR of the reaction is consistent with starting material plus product in about equal amounts plus some material on the baseline of the TLC. The material of the baseline of the TLC is separated from starting material and the product is extracted by acid/base extraction. The organic phase is dried and concentrated in vacuo to yield 73 g. The NMR and TLC are consistent with the formula




## EXAMPLE 4

73 g crude product of Example 3 is dissolved in 500 ml absolute THF and 120 ml triethyl borane is added, followed by 0.7 g t-butylcarboxylic acid. The mixture is stirred under a dry atmosphere for 10 minutes, cooled to −78° C. and 70 ml methanol is added and followed by 4.5 g sodium borohydride. The mixture is again stirred at −78° C. for six hours. Then poured slowly into a 4:1:1 mixture of ice/30% $H_2O_2/H_2O$. This mixture is stirred overnight then allowed to warm to room temperature.

$CHCl_3$ (400 ml) is added and the mixture is partitioned. The water layer is extracted again with $CHCl_3$. The organic extracts are combined and washed extensively with $H_2O$ until no peroxide could be found. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated.

The residue is treated by flash chromatography on silica gel, i.e. EtOAc/Hexane 1:3 to yield 51 g.

The product is dissolved in THF/MeOH and added to 100 ml in NaOH, then stirred for four hours at room temperature. The solution is concentrated at room temperature to remove organic solvent, added to 100 ml $H_2O$, and extracted with $Et_2O$ twice. The aqueous layer is acidified with 1N HCl and extracted with EtOAc three times. The combined organic layers are washed with $H_2O$. The organic layer is dried with anhydrous $MgSO_4$, filtered, and the solvent evaporated. The residue is taken up in 2 liters of toluene and heated to reflux using a Dean-Stark trap for 10 minutes.

The reaction mixture is allowed to cool to room temperature overnight. Reflux is repeated for 10 minutes and cooled for 24 hours.

The procedure above is repeated. The reaction is left at room temperature for the next 10 days, then concentrated to yield 51 g of colorless foam.

This product is dissolved in minimum $CHCl_3$ and chromatographed on silica gel eluting with EtOAc/-Heptane (50:50) to yield 23 g in pure material.

Chromatography on silica gel in $CHCl_3$/2-propanol (98.5:1.5) yields 13.2 g.

| Calc. |
|---|
| C: 73.31 |
| H: 6.15 |
| N: 5.18 |

## EXAMPLE 5

Preparation of 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H/-pyrrole-3-carboxamide

The product of Example 4 is recrystallized from EtOAc/Hexane. Fraction 1 yields 8.20 g of 4A. The mother liquor yields 4.60 g of 4B, HPLC of 4B shows 100% of the product to be the [R-(R*R*)] isomer. 4A is recrystallized to yield 4.81 g of 4C. 4B is chromatographed on silica gel in $CHCl_3$/2-propanol to yield 4.18 g colorless foam of 4D showing $\alpha_D^{23}+24.53°$ (0.53% in $CHCl_3$). 4C is recrystallized and the mother liquor of 4C is to yield 2.0 g.HPLC which indicates 100% of the R-trans isomer 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

## EXAMPLE 6

Preparation of diastereomeric α-methylbenzylamides

A solution of the racemate, trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, (30 g, 55.5 ml) in (R)-(+)-α-methylbenzylamine (575 ml, 4.45 mol, 98% Aldrich) is stirred overnight at room temperature.

The resulting solution is then diluted with ether (2 l) and then washed exhaustively with 2M HCl (4×500 ml), water (2×500 ml) and brine (2×500 ml). The organic extract is then dried over $MgSO_4$, filtered and concentrated in vacuo to yield 28.2 g of the diastereomeric α-methylbenzylamides as a white solid; m.p. 174.0°–177°. The α-methylbenzylamides are separated by dissolving 1.5 g of the mixture in 1.5 ml of 98:1.9:0.1 $CHCl_3$:$CH_3OH$:$NH_4OH$ (1000 mg/ml) and injecting onto a preparative HPLC column (silica gel, 300 mm×41.4 mm I.D.) by gastight syringe and eluting with the above solvent mixture. Fractions are collected by UV monitor. Diastereomer 1 elutes at 41 minutes. Diastereomer 2 elutes at 49 minutes. Center cut fractions are collected. This procedure is repeated three times and the like fractions are combined and concentrated. Examination of each by analytical HPLC indicates that diastereomer 1 is 99.84% pure and diastereomer 2 is 96.53% pure. Each isomer is taken on separately to following Examples.

## EXAMPLE 7

Preparation of 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

To an ethanolic solution (50M) of diastereomer 1 of Example 6, [3R-[3R*(R*),5R*]]-2-(4-fluorophenyl)-[β],[δ]- dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-N-(1-phenylethyl-1H-pyrrole-1-heptanamide, (hydroxy centers are both R) (1 g, 1.5 mmol) is added 1N NaOH (3.0 ml, 3 mmol). The resulting solution is heated to reflux for 48 hours.

The solution is cooled to room temperature and concentrated in vacuo. The residue is resuspended in water and carefully acidified with 6N HCl. The resulting acidic solution is extracted with ethyl acetate. The organic extract is washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. This residue is redissolved in toluene (100 ml) and heated to reflux with azeotropic removal of water for three hours. This is cooled to room temperature and concentrated in vacuo to yield 1.2 g of a yellow semi-solid. Flash chromatography on silica gel eluting with 40% EtOAc/-Hexane gives 0.42 g of a white solid which still contains impurities. This is rechromatographed to give 0.1 g of essentially pure R,R, enantiomer, 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, as a white foam. HPLC shows this material to be 94.6% chemically pure $[\alpha]_D^{23}$:0.51% in $CHCl_3$=25.5°. The peak at room temperature=53.46 minutes is tentatively assigned to an unknown diastereomer resulting from the 2% (S)-(−)-α-methylbenzylamine present in the Aldrich α-methylbenzylamine.

## EXAMPLE 8

Preparation of 2S-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide-(S,S enantiomer of the compound prepared in Example 5

Carrying out the procedure described in Example 7 on diastereomer 2 afforded 0.6 g of a foamy solid which was flash chromatographed on silica gel. Elution with 50% EtOAc/Hexane gave 0.46 g of essentially pure S,S, enantiomer 2S-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, as a white foam. HPLC showed this material to be 97.83% chemically pure. $[\alpha]_D^{23}$=0.51% in $CHCl_3$=−24.8%.

## EXAMPLE 9

Hydrolysis of chemical lactone of formula II

To a room temperature, solution of the lactone in THF is added a solution of sodium hydroxide in water. The mixture is stirred for two hours HPLC:99.6% (product); 0.34 to (starting lactone). The mixture is diluted with 3 L water, extracted with ethyl acetate (2×1 L) and acidified to pH×4 by addition of 37 ml of 5N hydrochloric acid. The aqueous layer is extracted with 2×1.5 L portions of ethyl acetate. The combined ethyl acetate extracts are washed with 2×1 L of water, brine and dried, gave after filtration the ethyl acetate solution of the required face-acid. This solution is used directly in the fraction of the N-methylglucamine salt.

The ethyl acetate extracts from the brine-water were concentrated to give 15.5 g of an off-white solid.

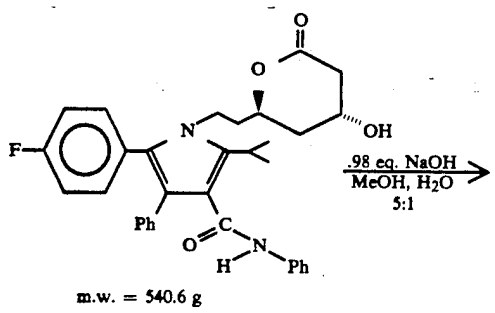
## EXAMPLE 10

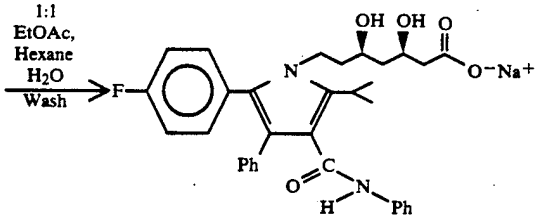
Calcium Salt from Sodium Salt and/or Lactone

Dissolve one mole lactone (540.6 g) in 5 L of MeOH; after dissolution add 1 L $H_2O$. While stirring, add one

equivalent NaOH and follow by HPLC until 2% or less lactone and methyl ester of the diolacid remains (cannot use an excess of NaOH, because $Ca(OH)_2$ will form an addition of $CaCl_2$). Charge NaOH as caustic (51.3 ml, 98 eq.) or as pellets (39.1 g, 0.98 eq.).

The above procedure is shown as follows:



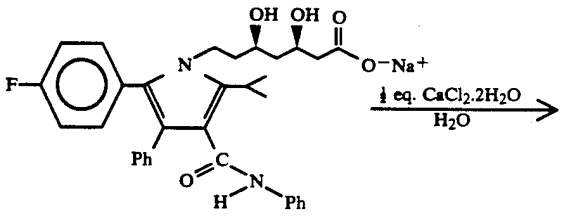




Upon completion of hydrolysis, add 10 L $H_2O$, then wash at least two times with a 1:1 mixture of EtOAc/-Hexane. Each wash should contain 10 L each of EtOAc/Hexane. If sodium salt is pure, add 15 L of MeOH. If it is impure and/or contains color, add 100 g of G-60 charcoal, stir for two hours and filter over supercel. Wash with 15 L MeOH. Perform a wt/vol % on the reaction mixture, by HPLC, to determine the exact amount of salt in solution.

Dissolve 1 eq. or slight excess $CaCl_2.2H_2O$ (73.5 g) in 20 L $H_2O$. Heat both reaction mixture and $CaCl_2$ solution to 60° C. Add $CaCl_2$ solution slowly, with high agitation. After complete addition, cool slowly to 15° C. and filter. Wash filter cake with 5 L $H_2O$. Dry at 50° C. in vacuum oven.

Can be recrystallized by dissolving in 4 L of EtOAc (50° C.) filtering over supercel, washing with 1 L EtOAc, then charging 3 L of hexane to the 50° C. rxn solution.

The above procedure is shown as follows:

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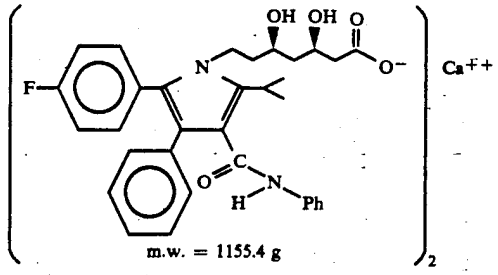


## EXAMPLE 11

Treatment of Ethyl Acetate Solution of Free-acid of the Formula I with N-methylglucamine

To a solution of the free-acid of the formula I (0.106M) in ethyl acetate (3 L) is added a solution of N-methylglucamine (20.3 g, 0.106 m) in (1:1) water-acetone (120 ml, 120 ml) with vigorous stirring at room temperature. Stirring is continued for 16 hours and the hazy solution concentrated in vacuo to ~250 mp. Toluene (1 L) is added and the mixture concentrated to a white solid ~100 g. The solid is dissolved in 1670 ml acetone and filtered into a three-neck flask equipped with a mechanical stirrer and thermostat controlled thermometer. The flask and filter is washed with 115 ml (1:1) water-acetone and the clear solution is cooled slowly. This provided a precipitate which is re-dissolved by heating back to 65° C. Addition of a further 20 ml of water followed by the washing gives a crystalline product which was isolated by filtration. The solids are washed with 1200 ml $CH_3Cl$ and vacuum dried at 255° to give a white solid. Analysis of this material indicates that it contains 4% amine as well as 0.4% residual acetone and 0.67% water. Analytical results are noted as follows:

Melting point: 105°–155° C. (decomposition) Analysis Expected: C=63.73; H-6.95; N=5.57; F2=9.53. Analysis Found: C=62.10; H-6.89; N-5.34; F2. C=61.92; H-7.02; N=5.38; F2.

$H_2O$=0.47% (KF)

HPLC: MeOH, $H_2O$, THF (40; 550; 250)
Econosil: C18, 5 μ, 25 CM
256 nm: 1.0 ml/min.
6–81 min.: 98.76%

Opt. Ret.: $[\alpha]\cdot b = -10.33°$ (c=1.00, MeOH)

Residual Solvents: $CH_2CH$=0.26%

Titrations:
$HClO_4$ (0.1N)=203.8%
$Bu_4NOH$ (0.1N)=98.5%

Other salts prepared in a manner analogous to those processes appropriately selected from Examples 10 and 11 above may be the potassium salt, hemimagnesium salt, hemizinc salt or the 1-deoxy-2-(methylamino)-D-glucitol complex of the compound of formula I.

I claim:

1. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β-δ-dihydroxy-5-(1-methylethyl)-3-phe-

nyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2.

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

* * * * *

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC, and WARNER-LAMBERT EXPORT, LTD., | : | |
| Plaintiffs, | : | |
| v. | : | Civil Action No. 03-209-JJF (Consolidated) |
| RANBAXY LABORATORIES LIMITED and RANBAXY PHARMACEUTICALS, INC., | : | |
| Defendants. | : | |

**O R D E R**

WHEREAS, the Court of Appeals for the Federal Circuit has issued its decision in the above-captioned appeal, affirming-in-part, reversing-in-part, and remanding this matter for modification of the permanent injunction; Pfizer Inc. v. Ranbaxy Laboratories Ltd., 457 F.3d 1284 (Fed. Cir. 2006);

WHEREAS, specifically, the Federal Circuit concluded that United States Patent No. 5,273,995 (the "'995 patent") was invalid for failure to comply with the requirements of 35 U.S.C. § 112, ¶ 4;

NOW THEREFORE, IT IS HEREBY ORDERED that, consistent with the Federal Circuit's decision, the last paragraph of the Final Judgment Order dated January 3, 2006, and entered by the Court on January 4, 2006, enjoining Defendants and others "from engaging in the manufacture, use, offer to sell, or sale within the United

States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claim 6 of the '995 Patent" is **STRICKEN**.

November 7, 2006
DATE

Joseph J. Farnan Jr.
UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

| | | |
|---|---|---|
| PFIZER INC., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC, and WARNER-LAMBERT EXPORT, LTD., | : | |
| Plaintiffs, | : | |
| v. | : | Civil Action No. 03-209-JJF (Consolidated) |
| RANBAXY LABORATORIES LIMITED and RANBAXY PHARMACEUTICALS, INC., | : | |
| Defendants. | : | |

**O R D E R**

WHEREAS, by Order dated November 7, 2006, the Court modified the Final Judgment Order entered on January 4, 2006, in light of the decision by the Court of Appeals for the Federal Circuit that United States Patent No. 5, 273, 995 (the "'995 patent) is invalid;

WHEREAS, it has come to the Court's attention that further modification of the Final Judgment Order is required;

WHEREAS, because the '995 patent has been declared invalid, a basis no longer exists to support delaying the approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 ("ANDA");

NOW THEREFORE, IT IS FURTHER ORDERED that the sixth paragraph of the Final Judgment Order delaying the effective date

of any approval of Ranbaxy's ANDA until a date not earlier than the expiration of the '995 patent is **STRICKEN**.

November 30 2006
DATE

Joseph J. Farnan Jr.
UNITED STATES DISTRICT JUDGE

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**CONFIDENTIAL**
**March 12, 2008**

**VIA FEDERAL EXPRESS DELIVERY**
Jeffrey B. Kindler,
Chairman and CEO
Pfizer, Inc
235 E. 42nd Street
New York, NY 10017

**VIA FEDERAL EXPRESS DELIVERY**
President
Warner-Lambert Company
201 Tabor Road
Morris Plains, NJ 07950

**Re: Patent Certification Notice – U.S. Patent Nos. 6,126,971, 5,969,156, 5,686,104 and 5,273,995**
**Atorvastatin Calcium Tablets, Eq. 10 mg Base, Eq. 20 mg Base and Eq. 40 mg Base**
**Teva Pharmaceuticals USA, Inc.'s ANDA 78-773**

Dear Mr. Kindler and/or Counsel:

Pursuant to 21 U.S.C. § 355(j)(2)(B) and Section 505(j)(2)(B)(ii) of the Food and Drug Act, Teva Pharmaceuticals USA, Inc. ("Teva USA"), a Delaware corporation with a principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454, hereby gives notice that Teva USA is, concurrently with this letter, submitting an amendment to Abbreviated New Drug Application No. 78-773 ("ANDA 78-773") for Teva USA's Atorvastatin Calcium Tablets, Eq. 10 mg Base, Eq. 20 mg Base and Eq. 40 mg Base ("Teva's Atorvastatin Tablets"), which contains the required bioavailability and/or bioequivalence data and a Paragraph IV certification (pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV)), which asserts that U.S. Patent Nos. 6,126,971("the '971 patent"),[1] 5,969,156 ("the '156 patent"),[2] 5,686,104 ("the '104 patent")[3] and 5,273,995 ("the '995 patent")[4] are invalid, unenforceable or not infringed.

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1 The FDA's Approved Drug Products With Therapeutic Equivalence Evaluations (the "Electronic Orange Book") lists the expiration date of the '971 patent as January 19, 2013 with pediatric exclusivity to July 19, 2013.

2 The FDA's Electronic Orange Book lists the expiration date of the '156 patent as July 8, 2016 with pediatric exclusivity to January 8, 2017.

3 The FDA's Electronic Orange Book lists the expiration date of the '104 patent as November 11, 2014 with pediatric exclusivity to May 11, 2015.

A detailed statement of the factual and legal bases for Teva USA's opinion regarding the '971, '156, '104 and '995 patents is provided. Teva USA reserves the right to assert additional grounds, reasons and authorities for its position that the aforesaid patents are invalid, unenforceable or not infringed.

An Offer of Confidential Access to Teva USA's ANDA 78-773, pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), accompanies this notice as a separate enclosure.

Sincerely,

Paul H. Fackler/GD

Paul H. Fackler, Ph.D.
Vice President, Global Generic Research & Development Biopharmaceutics

---

Enclosures: Teva Pharmaceuticals USA, Inc.'s Detailed Statement Of The Factual And Legal Bases Of Teva Pharmaceuticals USA, Inc.'s Opinion That U.S. Patent Nos. 6,126,971, 5,969,156, 5,686,104 And 5,273,995 Are Invalid, Unenforceable Or Not Infringed

Abbreviated New Drug Application 78-773 Offer Of Confidential Access Pursuant To 21 U.S.C. § 355(j)(5)(C)(i)(III)

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(continued...)

[4] The FDA's Electronic Orange Book lists the expiration date of the '995 patent as December 28, 2010 with pediatric exclusivity to June 28, 2011.

**Confidential: Teva Pharmaceuticals USA, Inc.'s Detailed Statement Of The Factual And Legal Bases Of Teva Pharmaceuticals USA, Inc.'s Opinion That U.S. Patent Nos. 6,126,971, 5,969,156, 5,686,104 And 5,273,995 Are Invalid, Unenforceable Or Not Infringed**

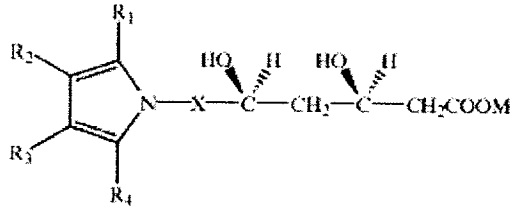


This is the detailed statement of Teva Pharmaceuticals USA, Inc. ("Teva USA"), pursuant to Section 505(j)(2)(B)(ii) of the Food and Drug Act (codified at 21 U.S.C. § 355(j)(2)(B)(ii), and 21 C.F.R. § 314.95(c)), of the factual and legal bases why U.S. Patent Nos. 6,126,971 ("the '971 patent"), 5,969,156 ("the '156 patent"), 5,686,104 ("the '104 patent") and 5,273,995 ("the '995 patent") are invalid, unenforceable or not infringed, either literally or under the doctrine of equivalents, by the manufacture, use, or sale of Teva USA's Atorvastatin Calcium Tablets, Eq. 10 mg Base, Eq. 20 mg Base and Eq. 40 mg Base ("Teva's Atorvastatin Tablets"), for which this detailed statement is submitted. Teva USA's factual and legal bases are set forth below.

## I. THE '971 PATENT

The '971 patent, entitled "Stable Oral CI-981 Formulation And Process For Preparing Same," issued on October 3, 2000 from U.S. Serial No. ("USSN") 08/886,982, filed July 2, 1997 as a continuation of USSN 08/246,919, filed May 20, 1994, now U.S. Patent No. 5,686,104, which is a continuation of USSN 08/005,708, filed January 19, 1993, now abandoned. The '971 patent is assigned on its face to Warner-Lambert Company.

The '971 patent issued with the following nineteen (19) claims, of which Claims 1, 4, 7, 8, 13, 16 and 17 are independent:

> 1. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, about 1% to about 50% by weight of the composition of a compound as active ingredient of structural formula I
>
> formula I
>
> 
> 

wherein X is —$CH_2$—, —$CH_2CH_2$—, —$CH_2CH_2CH_2$— or —$CH_2CH(CH_3)$I

$R_1$ is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either $R_2$ or $R_3$ is ——$CONR_5R_6$ where $R_5$ and $R_6$ are independently hydrogen; alkyl of from one to six carbon atoms; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of $R_2$ or $R_3$ is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

$R_4$ is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt; and

about 5% to about 75% by weight of the composition of calcium carbonate to stabilize the composition.

2. The stable pharmaceutical composition of claim 1, wherein M is a pharmaceutically acceptable alkaline earth metal salt.

**3**. The stable pharmaceutical composition of claim **2**, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

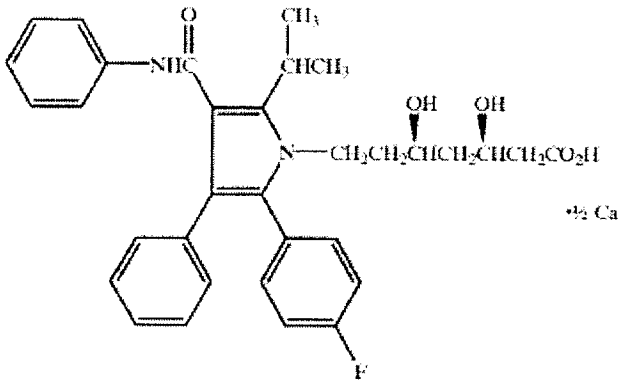
**4**. A pharmaceutical composition characterized by improved stability comprising in a mixture, about 1% to about 50% by weight of the composition of a pharmaceutically acceptable metal salt of [R—R*,R*)]-2-(4-fluorophenyl-β, A-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid; and about 5% to about 75% by weight of the composition of calcium carbonate to stabilize the composition.

**5**. The stable pharmaceutical composition of claim **4**, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

**6**. The stable pharmaceutical composition of claim **5**, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

7. A pharmaceutical composition characterized by improved stability comprising in a mixture, the Hemi-Calcium of Formula (IA):

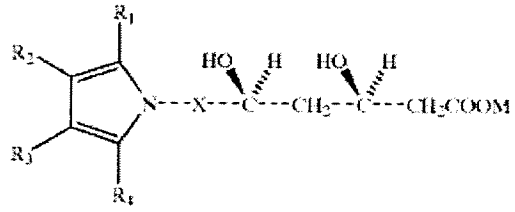
(IA)




and an effective amount of calcium carbonate.

8. A method of improving the stability of a pharmaceutical composition comprising as an active ingredient a compound having the structural formula I

formula I



wherein X is $—CH_2—$, $—CH_2CH_2—$, $—CH_2CH_2CH_2—$ or $—CH_2CH(CH_3)$;

$R_1$ is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either $R_2$ or $R_3$ is $——CONR_5R_6$ where $R_5$ and $R_6$ are independently hydrogen; alkyl of from one to six carbon atoms; 2-3- or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of $R_2$ or $R_3$ is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

$R_4$ is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt;

by adding an effective amount of an alkaline earth metal salt to the composition.

**9**. The method of claim **8**, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

**10**. The method of claim **9**, wherein the alkaline earth metal salt is calcium carbonate.

11. The method of claim 8, wherein M is a pharmaceutically acceptable alkaline earth metal salt.

12. The method of claim 11, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

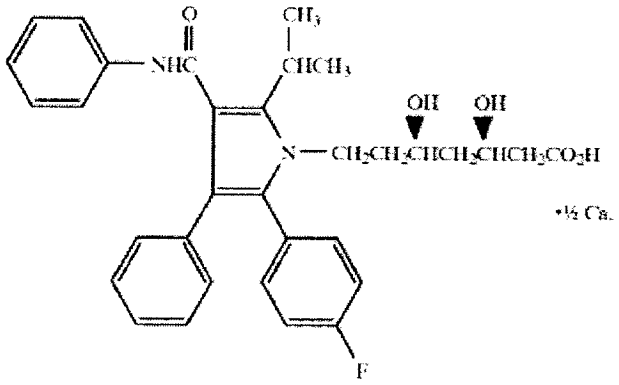
13. A method of improving the stability of a pharmaceutical composition by adding an effective amount of calcium carbonate to a composition comprising a pharmaceutically acceptable metal salt of [R—R*,R*)]-2-(4-fluorophenyl-β, δ-dihydroxy-5-(1 -methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1 heptanoic acid.

14. The method of claim 13, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

15. The method of claim 14, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

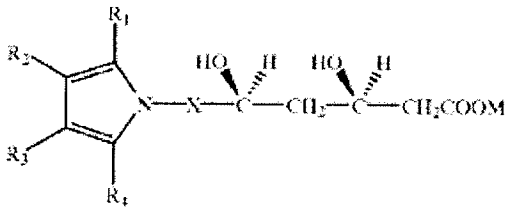
16. A method of improving the stability of a pharmaceutical composition by adding an effective amount of calcium carbonate to a composition comprising the Hemi-Calcium of Formula (IA):

(IA)




17. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, about 1% to about 50% by weight of the composition of a compound as active ingredient of structural formula I

formula I



wherein X is —$CH_2$—, —$CH_2CH_2$—, —$CH_2CH_2CH_2$— or —$CH_2CH(CH_3)$—

$R_1$ is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either $R_2$ or $R_3$ is —$CONR_5R_6$ where $R_5$ and $R_6$ are independently hydrogen; alkyl of from one to six carbon atoms; 2-,3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of $R_2$ or $R_3$ is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

$R_4$ is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt; and

about 5% to about 75% by weight of the composition of at least one stabilizing pharmaceutically acceptable calcium or lithium salt additive.

**18**. The stable pharmaceutical composition of claim **17** wherein the active ingredient is a pharmaceutically acceptable metal salt of [R—(R*,R*)]-2-(4-fluorophenyl-β, δ-dihydroxy-5(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid.

**19**. The stable pharmaceutical composition of claim **17** wherein the stabilizing pharmaceutically acceptable additive is a calcium salt.

## II. THE '156 PATENT

The '156 patent, entitled "Crystalline [R-(R*,R*)]-2-(4-Difluorophenyl)-β,δ-Dihydroxy-5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)carbonyl]-1H-Pyrrole-1-Heptanoic Acid Hemi Calcium Salt (Atorvastatin)" issued on October 19, 1999 from USSN 08/945,812, filed October 2, 1997 as a §371 national stage entry of PCT Application No. PCT/US96/11368, filed July 8, 1996, which published on February 6, 1997 as PCT International Application Publication No. WO 97/03959, and claiming the benefit of Provisional Application No. 60/001,452, filed July 17, 1995. The '156 patent is assigned on its face to Warner-Lambert Company.

The '156 patent issued with forty-four (44) claims on October 19, 1999. On September 26, 2006, an Ex Parte Reexamination Certificate was issued affirming the patentability of the originally issued claims, as amended, and adding new claims 45-117. Of the one-hundred-seventeen (117) claims, claims 1-9, 28-69, 100-110 and 113-117 are independent. Brackets indicate what was deleted from the originally issued claims and italics indicate what was added to the originally issued claims:

> 1. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing [at least one of] the following 2θ [values] *value* measured using $CuK_\alpha$ radiation: [11.9 or] 22.0.
>
> 2. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [$Cuk_\alpha$] *$CuK_\alpha$* radiation: 11.9, 21.6 and 22.0.
>
> 3. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 17.1, 19.5 and 21.6.
>
> 4. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [$Cuk_\alpha$] *$CuK_\alpha$* radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2.
>
> 5. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using [$Cuk_\alpha$] *$CuK_\alpha$* radiation: 9.150, 9.470, 10.266, 10.560, 11.853, 12.195, 17.075, 19.485, 21.626, 21.960, 22.748, 23.335, 23.734, 24.438, 28.915 and 29.234.
>
> 6. A crystalline Form I atorvastatin hydrate characterized by solid state $^{13}C$ nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 5.1 or 51.8.
>
> 7. A crystalline Form I atorvastatin hydrate characterized by solid state $^{13}C$ nuclear magnetic resonance and having

the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.

**8**. A crystalline Form I atorvastatin hydrate characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 18.9, 20.6, 26.1, 43.6, 46.8, 49.2, 51.8, 92.5, 96.9, 99.6, 102.2, 106.3, 108.2, 109.8, 113.6, 115.7, 138.0, 145.4, 157.1 and 161.5.

**9**. A crystalline Form I atorvastatin hydrate characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3[.], 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7, (broad), 178.4 and 182.8.

**10**. The crystalline Form I atorvastatin hydrate of claim **1** containing about 1 to 8 moles of water.

**11**. The crystalline Form I atorvastatin hydrate of claim **1** containing 3 moles of water.

**12**. The crystalline Form I atorvastatin hydrate of claim **2** containing about 1 to 8 moles of water.

**13**. The crystalline Form I atorvastatin hydrate of claim **2** containing 3 moles of water.

**14**. The crystalline Form I atorvastatin hydrate of claim **3** containing about 1 to 8 moles of water.

**15**. The crystalline Form I atorvastatin hydrate of claim **3** containing 3 moles of water.

**16**. The crystalline Form I atorvastatin hydrate of claim **4** containing about 1 to 8 moles of water.

**17**. The crystalline Form I atorvastatin hydrate of claim **4** containing 3 moles of water.

**18**. The crystalline Form I atorvastatin hydrate of claim **5** containing about 1 to 8 moles of water.

**19**. The crystalline Form I atorvastatin hydrate of claim **5** containing 3 moles of water.

**20**. The crystalline Form I atorvastatin hydrate of claim **6** containing about 1 to 8 moles of water.

**21**. The crystalline Form I atorvastatin hydrate of claim **6** containing 3 moles of water.

**22**. The crystalline Form I atorvastatin hydrate of claim **7** containing about 1 to 8 moles of water.

**23**. The crystalline Form I atorvastatin hydrate of claim **7** containing 3 moles of water.

**24**. The crystalline Form I atorvastatin hydrate of claim **8** containing about 1 to 8 moles of water.

**25**. The crystalline Form I atorvastatin hydrate of claim **8** containing 3 moles of water.

**26**. The crystalline Form I atorvastatin hydrate of claim **9** containing about 1 to 8 moles of water.

**27**. The crystalline Form I atorvastatin hydrate of claim **9** containing 3 moles of water.

**28**. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.0 [and]. 20.5 *and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad).*

**29**. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.5 [and]. 9.0 *and at least one value selected from the group consisting of 7.4, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad) and 25.7 (broad).*

**30**. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 5.6, 7.4, 8.5, 9.0, 12.4 (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad), 25.7 (broad) and 29.5.

**31**. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using [$Cuk_\alpha$] $CuK_\alpha$ radiation: 5.582, 7.384, 8.533, 9.040, 12.440 (broad), 15.771 (broad), 17.120–17.360 (broad), 19.490, 20.502, 22.706–23.159 (broad), 25.697 (broad) and 29.504.

**32**. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state $^{13}C$ nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 4.7 or 47.8.

**33**. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 44.5, 45.2, 46.2 and 47.8.

**34**. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 17.4, 18.9, 19.5, 20.6, 44.5, 45.2, 46.2, 47.8, 91.9, 92.9, 94.3, 96.2, 97.5, 98.6, 100.1, 106.2, 110.5, 112.0, 117.7, 138.2, 140.2 and 158.2.

**35**. Crystalline Form II atorvastatin or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).

**36**. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing [at least one of] the following 2θ values measured using $CuK_\alpha$ radiation: 8.0 [or], 9.7 *and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.*

**37**. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0 and 9.7.

**38**. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0, 9.7 [and], 19.6 *and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.*

**39**. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 5.4, 5.9, 8.0, 9.7, 10.4, 12.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1.

**40**. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.889, 5.424, 5.940, 7.997, 9.680, 10.416, 12.355, 17.662, 18.367, 19.200, 19.569, 21.723, 23.021, 23.651 and 24.143.

**41**. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state $^{13}C$ nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 8.0 or 53.6.

**42**. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 45.6, 48.4, 50.0 and 53.6.

**43**. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 1.5, 2.4, 8.0, 22.1, 24.2, 25.5, 28.2, 45.6, 48.4, 50.0, 53.6, 97.8, 101.9, 104.8, 109.2, 111.3, 116.8, 120.2, 141.1, 148.2, 161.4, 163.5, 167.0 and 168.5.

**44**. Crystalline Form IV atorvastatin or a hydrate thereof characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1,129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.

*45. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 11.9 and 22.0.*

*46. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0 and at least one value selected from the group consisting of 4.9, 5.4, 10.4, 12.4, 18.4, 19.2, 21.7, 23.0 and 24.1.*

*47. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 17.1, 19.5, 21.6 and at least one value selected from the group consisting of 9.2, 10.3, 11.9, 12.2, 22.0, 22.7, 23.7, 24.4, 28.9 and 29.2.*

*48. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0 and 12.4.*

*49. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0, 9.7 and 12.4.*

*50. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0, 9.7 and at least one value selected from the group consisting of 5.4, 5.9, 10.4, 12.4, 17.7, 19.6 and 23.7.*

*51. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0, 9.7, 19.6 and at least one value selected from the group consisting of 4.9, 12.4 and 21.7.*

*52. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6 and 22.0.*

*53. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6 and 11.9.*

*54. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 21.6 and 22.0.*

*55. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 17.1, 19.5 and 21.6.*

*56. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad), 17.1–17.4 (broad) and 20.5.*

*57. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad) and 17.1–17.4 (broad).*

*58. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0, 9.7 and 12.4.*

*59. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0, 9.7, 12.4 and at least one value selected from the group consisting of 5.4, 5.9, 10.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1.*

*60. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0, 9.7, 12.4 and 19.6.*

*61. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 11.9; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.*

*62. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 5.1.*

*63. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having a chemical shift difference between the lowest ppm resonance and another resonance of 51.8.*

*64. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 3.9, 5.1, 43.6, 46.8, 49.2 and 51.8.*

*65. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2 and 11.9; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift expressed in parts per million: 182.8.*

*66. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2 and 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift expressed in parts per million: 182.8.*

*67. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 11.9; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.*

*68. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.*

*69. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 11.9 and 22.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.*

*70. The crystalline Form I atorvastatin hydrate of claim 45 containing about 1 to 8 moles of water.*

*71. The crystalline Form I atorvastatin hydrate of claim 47 containing about 1 to 8 moles of water.*

*72. The crystalline Form I atorvastatin hydrate of claim 52 containing about 1 to 8 moles of water.*

*73. The crystalline Form I atorvastatin hydrate of claim 53 containing about 1 to 8 moles of water.*

*74. The crystalline Form I atorvastatin hydrate of claim 54 containing about 1 to 8 moles of water.*

*75. The crystalline Form I atorvastatin hydrate of claim 55 containing about 1 to 8 moles of water.*

*76. The crystalline Form I atorvastatin hydrate of claim 61 containing about 1 to 8 moles of water.*

*77. The crystalline Form I atorvastatin hydrate of claim 62 containing about 1 to 8 moles of water.*

*78. The crystalline Form I atorvastatin hydrate of claim 63 containing about 1 to 8 moles of water.*

*79. The crystalline Form I atorvastatin hydrate of claim 64 containing about 1 to 8 moles of water.*

*80. The crystalline Form I atorvastatin hydrate of claim 65 containing about 1 to 8 moles of water.*

*81. The crystalline Form I atorvastatin hydrate of claim 66 containing about 1 to 8 moles of water.*

*82. The crystalline Form I atorvastatin hydrate of claim 67 containing about 1 to 8 moles of water.*

*83. The crystalline Form I atorvastatin hydrate of claim 68 containing about 1 to 8 moles of water.*

*84. The crystalline Form I atorvastatin hydrate of claim 69 containing about 1 to 8 moles of water.*

*85. The crystalline Form I atorvastatin hydrate of claim 45 containing 3 moles of water.*

*86. The crystalline Form I atorvastatin hydrate of claim 47 containing 3 moles of water.*

*87. The crystalline Form I atorvastatin hydrate of claim 52 containing 3 moles of water.*

*88. The crystalline Form I atorvastatin hydrate of claim 53 containing 3 moles of water.*

*89. The crystalline Form I atorvastatin hydrate of claim 54 containing 3 moles of water.*

*90. The crystalline Form I atorvastatin hydrate of claim 55 containing 3 moles of water.*

*91. The crystalline Form I atorvastatin hydrate of claim 61 containing 3 moles of water.*

*92. The crystalline Form I atorvastatin hydrate of claim 62 containing 3 moles of water.*

*93. The crystalline Form I atorvastatin hydrate of claim 63 containing 3 moles of water.*

*94. The crystalline Form I atorvastatin hydrate of claim 64 containing 3 moles of water.*

*95. The crystalline Form I atorvastatin hydrate of claim 65 containing 3 moles of water.*

*96. The crystalline Form I atorvastatin hydrate of claim 66 containing 3 moles of water.*

*97. The crystalline Form I atorvastatin hydrate of claim 67 containing 3 moles of water.*

*98. The crystalline Form I atorvastatin hydrate of claim 68 containing 3 moles of water.*

*99. The crystalline Form I atorvastatin hydrate of claim 69 containing 3 moles of water.*

*100. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift difference between the lowest ppm resonance and another resonance of 4.7.*

*101. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4,*

*8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift difference between the lowest ppm resonance and another resonance of 47.8.*

*102. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shift differences between the lowest ppm resonance and other resonances: 4.7, 44.5, 45.2, 46.2 and 47.8.*

***103. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.0, 20.5 and at least one value selected from the group consisting of 5.6, 7.4, 8.5, 15.8 (broad) and 25.7 (broad); and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).***

***104. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.5 and 9.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 140.5 and 181 (broad).***

***105. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.5, 9.0 and at least one value selected from the group consisting of 7.4, 12.4, (broad), 15.8 (broad), 17.1–17.4 (broad), 19.5, 20.5, 22.7–23.2 (broad) and 25.7 (broad); and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 140.5 and 181 (broad).***

*106. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ value measured using $CuK_\alpha$ radiation: 8.0; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.*

*107. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0 and 9.7; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.*

*108. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 8.0 and 9.7; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.*

*109. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 8.0, 9.7 and 19.6; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 127.1, 184.9 and 186.4.*

*110. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 11.9, 12.2, 17.1, 19.5, 21.6, 22.0, 22.7, 23.3, 23.7, 24.4, 28.9 and 29.2; and further characterized by solid-state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 21.3, 25.2, 26.4, 40.2, 41.9, 47.4, 64.9, 68.1, 70.5, 73.1, 113.8, 118.2, 120.9, 123.5, 127.6, 129.5, 131.1, 134.9, 137.0, 159.3, 166.7 (broad), 178.4 and 182.8.*

*111. The crystalline Form I atorvastatin hydrate of claim 110 containing about 1 to 8 moles of water.*

*112. The crystalline Form I atorvastatin hydrate of claim 110 containing 3 moles of water.*

*113. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 5.6, 7.4, 8.5, 9.0, 12.4 (broad), 15.8 (broad), 17.1-17.4 (broad), 19.5, 20.5, 22.7-23.2 (broad), 25.7 (broad) and 29.5; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 22.8 (broad), 27.5, 40.2, 41.7, 42.3, 43.4, 67.3, 68.0, 69.0, 70.6, 114.7, 115.7, 117.1, 119.0, 120.3, 121.4, 122.9, 129.0, 133.3, 134.8, 140.5, 161 (broad), 163 (broad) and 181 (broad).*

*114. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 5.4, 5.9, 8.0, 9.7, 10.4, 12.4, 17.7, 18.4, 19.2, 19.6, 21.7, 23.0, 23.7 and 24.1; and further characterized by solid state $^{13}C$ nuclear magnetic resonance having the following chemical shifts expressed in parts per million: 17.9, 19.4, 20.3, 25.9, 40.0, 42.1, 43.4, 46.1, 63.5, 66.3, 67.9, 71.5, 115.7, 119.8, 122.7, 127.1, 129.2, 134.7, 138.1 (broad), 159.0 (broad), 166.1 (broad), 179.3, 181.4, 184.9 and 186.4.*

*115. A crystalline Form I atorvastatin hydrate having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 9.2, 9.5, 10.3, 10.6, 11.9 and 12.2.*

*116. Crystalline Form II atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 5.6, 8.5, 9.0, 12.4 (broad), 15.8 (broad) and 17.1-17.4 (broad).*

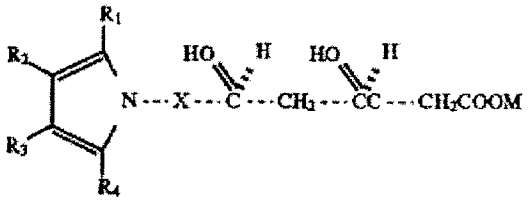
*117. Crystalline Form IV atorvastatin or a hydrate thereof having an X-ray powder diffraction containing the following 2θ values measured using $CuK_\alpha$ radiation: 4.9, 5.4, 8.0 and 12.4.*

## III. THE '104 PATENT

The '104 patent, entitled "Stable Oral CI-981 Formulation And Process For Preparing Same," issued on November 11, 1997 from USSN 08/246,919, filed May 20, 1994, which is a continuation of USSN 08/005,708, filed January 19, 1993, now abandoned. The '104 patent is assigned on its face to Warner-Lambert Company.

The '104 patent issued with the following twenty-two (22) claims, of which Claims 1, 14, 15 and 21 are independent:

**1.** A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, a compound as active ingredient of structural formula I




wherein X is $—CH_2—$, $—CH_2CH_2—$, $—CH_2CH_2CH_2—$ or $—CH_2CH(CH_3)$;

$R_1$ is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with flourine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either $R_2$ or $R_3$ is $—CONR_5R_6$ where $R_5$ and $R_6$ are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other $R_2$ or $R_3$ is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

$R_4$ is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt;

at least one stabilizing pharmaceutically acceptable alkaline metal salt additive and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

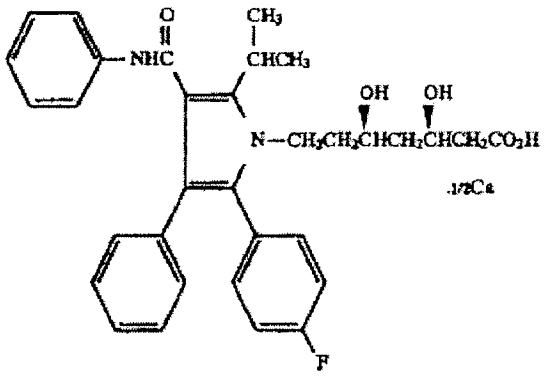
at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%.

2. The stable pharmaceutical composition of claim 1 wherein the active ingredient is a pharmaceutically acceptable metal salt of [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid.

3. The stable pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

4. The stable pharmaceutical composition of claim 2, wherein the active ingredient is CI-981 Hemi-Calcium of Formula (IA):




(IA)

and wherein the stabilizing pharmaceutically acceptable metal salt additive is calcium carbonate.

5. The stable pharmaceutical composition of claim 1, 2 or claim 4, wherein the active ingredient dosage is between about 1% and about 50% by weight of the composition.

6. A method for preparing a stable pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia comprising a step of mixing thoroughly about 1% to about 50% by weight of the active ingredient of claim 1, claim 2 or claim 4 with about 5% to about 75% by weight of a stabilizing pharmaceutically acceptable additive.

7. The stable pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

8. The stable pharmaceutical composition of claim 1 wherein the stabilizing pharmaceutically acceptable metal salt additive is an alkaline earth metal salt.

9. The stable pharmaceutical composition of claim 8, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

10. The stable pharmaceutical composition of claim 1, wherein the stabilizing pharmaceutically acceptable metal salt additive is calcium carbonate.

11. The stable pharmaceutical composition of claim 10 wherein the stabilizer calcium carbonate is in the range from about 5% to about 75% by weight of the composition.

12. The stable pharmaceutical composition of claim 1, further comprising an antioxidant.

13. The stable pharmaceutical composition of claim 12 wherein the composition comprises by weight between about 5% and about 75% microcrystalline cellulose; between about 1% and about 80% of hydrous lactose; between about 1% and about 15% of croscarmellose sodium; between about 0.5% and about 6% hydroxypropyl cellulose; between about 0.1% and about 4% of Tween 80; between about 0.25% and about 2% of magnesium stearate; and up to about 3% of sodium ascorbate or butylated hydroxyanisole of the total solid composition.

14. A stabilized solid pharmaceutical composition for peroral treatment of hypercholesterolemia or hyperlipidemia comprising in solid unit dosage form an active ingredient [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1 H-pyrrole-1-heptanoic acid hemicalcium salt and a stabilizer selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

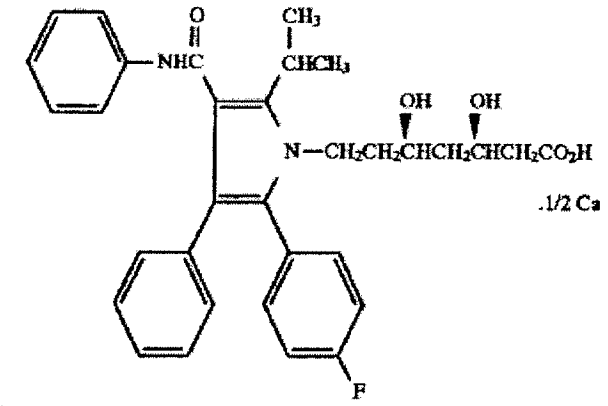
at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%.

15. A method for preparing a stabilized pharmaceutical composition formulated for peroral therapy of hypercholesterolemia or hyperlipidemia comprising:

(a) milling an excess of the drug, CI-981 Hemi-Calcium of the formula IA:




(b) dissolving at least one binder additive in aqueous surfactant solution;

(c) blending the milled drug with at least one drug-stabilizing alkaline earth metal salt additive and at least one diluent additive ingredient with the drug-stabilizing additive and one half of a disintegrant additive in a rotary mixing vessel equipped with a chopping device;

(d) granulating the blended drug mixture of step (c) with the surfactant/binder solution of step (b) in gradual increments in the chopper equipped mixing vessel;

(e) drying the granulated drug mixture overnight at about 50° C.;

(f) sieving the dried granulated drug mixture;

(g) tumble blending the sieved drug mixture with the remaining amount of the disintegrant additive;

(h) mixing separately an aliquot of the step (g) drug mixture with magnesium stearate, sieving same, and returning same to the drug mixture of step (g) and tumble blending the entire drug mixture; and compressing aliquots of the step (h) drug mixture into tablets.

16. The method claimed in claim 15, wherein in step (c) the drug stabilizing additive comprises a basic inorganic salt of calcium or magnesium.

17. The method claimed in claim 15, wherein in step (b) the binder additive comprises methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol or starch; and the surfactant comprises Tween 80 or polyoxyethylene-polyoxypropylene copolymer.

18. The method of claim 15 wherein in step (c) the disintegrant additive comprises croscarmellose sodium, carboxymethyl cellulose calcium or starch.

**19.** The method claimed in claim **15** wherein in step (c) the diluent additive is selected from the group consisting of microcrystalline cellulose, hydrous lactose, corn starch, sucrose, silicic anhydride and mixtures thereof.

**20.** The method claimed in claim **15** wherein the diluent additive is at least one polysaccharide.

**21.** A peroral pharmaceutical composition for treating hypercholesterolemia comprising an effective, cholesterol synthesis inhibitory amount of the enantiomer [R-R*,R*)]-2(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt; stabilized by calcium carbonate, and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%, in a dosage of solid enantiomer ranging from about 0.1 to about 8.0 mg/kg body weight per day.

**22.** A method of treating hypercholesterolemia or hyperlipidemia comprising a therapeutically effective unit dosage of the peroral pharmaceutical composition of claim **21** in the form of tablets or capsules.

## IV. THE '995 PATENT

The '995 patent, entitled "[R-(R*R*)]-2-(4-Fluorophenyl)-β,δ-Dihydroxy-5-(1-Methylethyl-3-Phenyl-4-[(Phenylamino)carbonyl]-1H-Pyrrole-1-Heptanoic Acid, Its Lactone Form And Salts Thereof" issued on December 28, 1993 from USSN 08/660,976, filed February 26, 1991 as a continuation of USSN 08/384,187, filed July 21, 1989, now abandoned. The '995 patent is assigned on its face to Warner-Lambert Company.

The '995 patent issued with the following twelve (12) claims, of which only claim 1 is independent:

> **1.** [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or pharmaceutically acceptable salts thereof.
>
> **2.** A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β-δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.
>
> **3.** A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.
>
> **4.** The monosodium salt of the compound of claim 2.
>
> **5.** The monopotassium salt of the compound of claim 2.
>
> **6.** The hemicalcium salt of the compound of claim 2.
>
> **7.** The N-methylglucamine salt of the compound of claim 2.
>
> **8.** The hemimagnesium salt of the compound of claim 2.
>
> **9.** The hemizinc salt of the compound of claim 2.
>
> **10.** The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.
>
> **11.** A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
>
> **12.** A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

## V. LEGAL PRINCIPLES

### A. Invalidity

#### 1. Anticipation Under 35 U.S.C. § 102(a)/(b)

Anticipation under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single prior art reference. *See Brown v. 3M*, 265 F.3d 1349, 1352 (Fed. Cir. 2001); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001). Anticipation is a question of fact. *Brown*, 265 F.3d at 1351.

Under 35 U.S.C. § 102(a), anticipation arises when:

> The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent ....

Under 35 U.S.C. § 102(b), anticipation arises when:

> the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States ....

An invention is not novel, and is therefore anticipated, if a prior art reference discloses every element of the asserted invention, either expressly or inherently. *See, e.g., Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) ("[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference."). Moreover, inherent anticipation does not require that the inherent characteristic be recognized in the prior art. *E.g., Id.* (citing *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002)). "Our cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time." *Abbott Labs. v. Baxter Pharm. Prods., Inc.* 471 F.3d 1363, 1367 (Fed. Cir. 2006).

Inherent anticipation does not require that the inherent characteristic invariably result from every attempt to practice the prior art. Instead, where the "natural result flowing from the operation as taught" in the prior art would be the invention claimed in the patent-in-suit, that invention is inherently anticipated. *See Finnigan Corp. v. United States Int'l Trade Comm'n*, 180 F.3d 1354, 1365 (Fed. Cir. 1999) (*quoting Continental Can*, 948 F.2d at 1268-69); *Eli Lilly and Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)).

A disclosure of a genus is sufficient to describe a species of the genus, provided the genus includes a preferred limited number of members. *In re Sivaramakrishnan*, 673 F.2d 1383, 1385 (C.C.P.A. 1982); *In re Schaumann*, 572 F.2d 312, 316 (C.C.P.A. 1978); *In re Petering*, 301

F.2d 676, 681 (C.C.P.A. 1962). For example, in *In Re Petering*, the Court held that the prior art teaching that a certain class of compounds within a large genus was preferred, was sufficient to describe and thus anticipate each of the 20 members of the class of compounds.

To anticipate a claim, the prior art reference must contain an enabling disclosure. *See In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985) (holding that a non-enabled disclosure will not suffice as § 102 prior art).

**2. Obviousness Under 35 U.S.C. § 103**

A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 35 U.S.C. § 103. The objective standard for determining obviousness under 35 U.S.C. §103, as set forth in *Graham v. John Deere, Co.*, 383 U.S. 1 (1966), requires a factual determination to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the claimed subject matter and the prior art. Based on these factual inquiries, it must then be determined, as a matter of law, whether or not the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the alleged invention was made. *Id.* at 17.

In determining obviousness under 35 U.S.C. § 103, "the test is whether the combined teachings of the prior art, taken as a whole, would have rendered the claimed invention obvious to one of ordinary skill in the art." *In re Napier*, 55 F.3d 610, 613 (Fed. Cir. 1995) (citation omitted). From the teachings, the prior art must create a reasonable expectation, not an absolute prediction, of success in producing the claimed invention. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("Indeed, a rule of law equating unpredictability to patentability . . . cannot be the proper standard since the expectation of success need only be reasonable, not absolute.").

> *Obviousness does not require absolute predictability of success.* Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *For obviousness under § 103, all that is required is a reasonable expectation of success.*

*In re O'Farrell*, 853 F.2d. 894, 903-904 (Fed. Cir. 1988) (emphasis added) (internal citations omitted). Both the suggestion and the expectation of success must be in the prior art, not in applicant's disclosure. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207 (Fed. Cir. 1991) (citing *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)).

A claim may be proven obvious in view of a single prior art reference or in view of a combination of prior art references. When the prior art references are combined to invalidate a claim under 35 U.S.C. § 103, there must be some teaching, suggestion or motivation in the prior art to do so. That teaching, suggestion or motivation ("TSM") need not be expressly stated in one or all of the references used to show obviousness, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006); *see also Cable Elec. Prods. Inc. v. Genmark, Inc.*, 770 F.2d. 1015, 1025 (Fed. Cir. 1985); *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992). Moreover, "the [TSM] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007).

"In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls." *Id.* at 1741-42; *see also Beattie*, 974 F.2d at 1312. "The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." *KSR*, 127 S.Ct. at 1742. "Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.*

Thus, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 1739. Furthermore, under some circumstances, obviousness under § 103 may be proved merely by showing that a combination of elements was 'obvious to try':

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that is was obvious under § 103.

*Id.* at 1742. "[W]hile patentability of an invention is not negated by the manner in which it was made, 'the converse is equally true: patentability is not imparted where 'the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.'" *See Pfizer,* 480 F.3d at 1369 (discussing obvious-to-try and routine experimentation in the context of obviousness under 35 U.S.C. § 103) (internal citations omitted).

In the case of pharmaceutical salts, where the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan, reasonably suggests that reacting a drug with a known pharmaceutically acceptable acid would form the acid addition salt, routine

testing to verify the expected physicochemical characteristics of that salt (*e.g.*, solubility, pH, stability, hygroscopicity and stickiness) does not compel a conclusion of non-obviousness. *Id.* at 1367-68 (holding claims to amlodipine besylate salt to be invalid as obvious, stating "our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation").

In the case of enantiomers and racemic mixtures, in *Aventis Pharma. Deutschland v. Lupin Ltd. et al.*, 499 F.3d 1293 (Fed. Cir. 2007) the Federal Circuit stated, "[I]f it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that this is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified." *Id.* at 1301 (internal citations omitted). The Federal Circuit thus found that claims which covered the 5(S) stereoisomer of ramipril in a composition substantially free of other isomers were invalid as obvious over the prior art disclosure of mixtures of the stereoisomers. *Id.* at 1303. In its decision, the court distinguished *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007) in which the court found "that prima facie obviousness of a claim to a particular stereoisomer over a racemic mixture was rebutted where the particular stereoisomer showed unexpected benefits and evidence indicated that the isomers would have been difficult for a person of ordinary skill in the art to separate." *Id.*

Secondary considerations of nonobviousness, such as commercial success, long-felt but unsolved needs, failure of others, and unexpected results, if present, must also be considered. *Stratoflex,* 713 F.2d at 1538-39. These secondary considerations, however, do not control the analysis when there is an otherwise strong case of obviousness, such as one based upon prior art not considered by the PTO during prosecution. *Pfizer,* 480 F.3d at 1372 (citing *Newell Cos, Inc. v. Kenny Mfg. Co.*, 864 F.2d 757, 768-69 (Fed. Cir. 1988)).

For a claimed invention's commercial success to be given substantial weight, a nexus must be established between the merits of the claimed invention and the commercial success. *Cable Elec.*, 770 F.2d. at 1027; *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006).

> Thus, if the commercial success is due to an unclaimed feature of the device, the commercial success is irrelevant. So too, if the feature that creates the commercial success was known in the prior art, the success is not pertinent.

*Ormco*, 463 F.3d at 1312. The patentee bears the burden of establishing a *prima facie* case of such a nexus. *Demaco Corp. v. F. Von Langsdorf Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988).

Unexpected results, such as an unexpectedly superior property or unexpected synergy resulting from a combination of elements, may be considered as evidence of nonobviousness.

This requires the court to first consider what was expected. *Pfizer,* 480 F.3d at 1371 (citation omitted). Additionally, the Federal Circuit has stated that "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). In general, subject matter arrived at through routine optimization that works for its intended purpose is not patentable, even if it is better or more desirable than the prior art, unless it is unexpectedly superior. *See Pfizer,* 480 F.3d at 1371 ("The fact that amlodipine besylate was the best of the seven acid addition salts *actually tested* proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art.").

### 3. Invalidity Based On Obviousness-Type Double Patenting

The doctrine of double patenting is intended to prevent a patentee from obtaining a time-wise extension of patent exclusivity beyond the statutory term of a patent. *See Perricone v. Medicis Pharm. Corp.,* 432 F.3d 1368, 1372 (Fed. Cir. 2005); *In re Lonardo*, 119 F.3d 960, 965 (Fed. Cir. 1997); *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279-80 (Fed. Cir. 1992); *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985) ("A double patenting rejection precludes one person from obtaining more than one valid patent for either (a) the 'same invention,' or (b) an 'obvious' modification of the same invention.").

Obviousness-type double patenting is a judicially created doctrine that extends the statutory principles of same invention double patenting to "merely obvious variants of what has been patented." *Gen. Foods*, 972 F.2d at 1280 (emphasis omitted); *see also Perricone*, 432 F.3d at 1372-73; *Geneva Pharms., Inc., v. GlaxoSmith Kline plc*, 349 F.3d 1373, 1378 (Fed. Cir. 2003). Obviousness-type double patenting cements the legislative intent to limit a patentee's right to exclude by prohibiting a party from obtaining an extension of that right through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent. *Eli Lilly & Co. v Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001); *Gerber Garment Tech., Inc., v. Lectra Sys., Inc.*, 916 F.2d 683, 686 (Fed. Cir. 1990) (explaining that obviousness-type double patenting is "adopted out of necessity where the courts were faced with a situation in which claims in two applications or patents were not drawn precisely to the same invention, but were drawn to inventions so very much alike as to render one obvious in view of the other").

Obviousness-type double patenting is an affirmative defense, which, like other invalidity challenges, must be proved by clear and convincing evidence. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991); *see also Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999) ("Under obviousness-type double patenting, a patent [claim] is invalid when it is merely an obvious variation of an invention disclosed and claimed in an earlier patent by the same [patentee]."). When an obviousness-type double patenting attack is made against a granted patent, the Federal Circuit has held that "the double patenting challenge must be evaluated, like any other ground of invalidity, against individual claims." *Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 942 (Fed. Cir. 1992). Double patenting is a matter of what is claimed and so, like claim construction, is a question of law which the Federal Circuit reviews *de*

*novo*. *Geneva Pharms.*, 349 F.3d at 1377; *Georgia-Pacific*, 195 F.3d at 1326; *Gen. Foods*, 972 F.2d at 1275 ("The law of double patenting is concerned only with what patents claim.").

The Federal Circuit has outlined a two-step approach to analyzing obviousness-type double patenting. *Eli Lilly*, 251 F.3d at 968. "First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences." *Id.*; *see also Perricone*, 432 F.3d at 1375 ("This court first examines the contention that the claims of [one patent] contain 'material differences' from [another]."). "Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Eli Lilly*, 251 F.3d at 968; *Georgia-Pacific*, 195 F.3d at 1327-29. "A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim." *Eli Lilly*, 251 F.3d at 968; *see also In re Berg*, 140 F.3d 1428, 1437 (Fed. Cir. 1998) (affirming an obviousness-type double patenting rejection where a pending patent claim to a genus was anticipated by an earlier patent claim to a species within that genus). In evaluating whether a claim is obvious, the court inquires "whether the claimed invention in the application for the second patent would have been obvious from the subject matter of the claims in the first patent, in light of the prior art." *In re Longi*, 759 F.2d 887, 893 (C.C.P.A. 1985) (internal citations omitted).

### B. Non-Infringement

A person is a direct infringer under 35 U.S.C. § 271(a) if that person makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention, without authorization of the patent holder. Direct infringement may be either literal or under the doctrine of the equivalents.

#### 1. Literal Infringement

Literal infringement of a patent claim requires that the accused device contain each and every limitation recited in the claim. *See Carroll Touch, Inc. v. Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1579 (Fed. Cir. 1993). If there is any deviation or if any limitation is missing, there can be no literal infringement as a matter of law. *Lantech, Inc. v. Keip Mach. Co.*, 32 F.3d 542 (Fed. Cir. 1994).

#### 2. Infringement Under The Doctrine Of Equivalents

Under the doctrine of equivalents, "a product or process that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 117 S. Ct. 1040, 1049 (1997). If the difference between an element of the accused product or process and a claimed element of the patented invention is not insubstantial, there is no infringement under the doctrine of equivalents. *See Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512 (Fed. Cir. 1995) (*en banc*), *rev'd on other grounds*, 117 S. Ct. 1040 (1997).

However, several principles limit the use of the doctrine of equivalents to find infringement. For example, application of the doctrine of equivalents does not allow "such broad play as to effectively eliminate [a claim] element in its entirety." *Warner-Jenkinson*, 117 S. Ct. at 1049.

### 3. Determination Of Infringement

To determine whether a product infringes a United States patent, there is a two-step inquiry in which the court: (1) construes the claim; and (2) compares the properly construed claim to the accused device or process. *Carroll Touch*, 15 F.3d at 1576.

When construing a claim the court should rely on the claim language, the specification, the prosecution history, and if necessary to aid the court's understanding of the patent, extrinsic evidence. *See Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302 (Fed. Cir. 2000); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1500 (Fed. Cir. 1998).

### 4. Inducement Of Infringement And Contributory Infringement

A person induces infringement under 35 U.S.C. § 271(b) by actively and knowingly aiding and abetting another's direct infringement. *C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc.*, 911 F.2d 670, 675 (Fed. Cir. 1990). However: "If a physician, without inducement by [an alleged infringer], prescribes a [product] in an infringing manner, [the alleged infringer's] knowledge is legally irrelevant." *Warner-Lambert v. Apotex*, 316 F.3d 1348, 1364 (Fed. Cir. 2003).

Contributory infringement requires that a party offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non-infringing use. *See* 35 U.S.C. § 271(c).

For inducement and contributory infringement, direct infringement of the patent claims, either literally or under the doctrine of equivalents, must be found. *Aro Mfg. Co. v. Convertible Top Replacement Co., Inc.*, 365 U.S. 336, 341 (1961).

## VI. TEVA'S ATORVASTATIN TABLETS WILL NOT INFRINGE ANY VALID AND ENFORCEABLE CLAIM OF THE '971 PATENT

### A. Claims 1-7, 10 And 13-19 Are Not Infringed

#### 1. Claims 1-3 Are Not Infringed

Claim 1 states, in part, a pharmaceutical composition comprising a compound of structural formula I and "about 5% to about 75% by weight of … calcium carbonate to stabilize the composition."

The Teva Atorvastatin Tablets do not contain the claimed calcium carbonate. Accordingly, for at least this reason, the Teva Atorvastatin Tablets cannot literally infringe Claim 1.

Moreover, only the filler and disintegrant in the Teva Atorvastatin Tablets are present in amounts which exceed the minimum amount of stabilizer required by Claim 1, *i.e.* 5%, and they are not classified as stabilizers. The remaining excipients are present in amounts which are substantially less than 5% by weight of the tablet. Consequently, even if any of the remaining excipients in the Teva Atorvastatin Tablets functioned as a stabilizer, they could not be an equivalent of "about 5% to about 75%" of stabilizer as required by Claim 1. *Tegal Corp. v. Tokyo Electron Co.*, 2002 U.S. App. Lexis 1992 (Fed. Cir. Feb. 1, 2002) (unpublished opinion) (2 MHz not equivalent of 1 MHz because 2 MHz is twice 1 MHz and finding of equivalence would vitiate that limitation).

In addition, a hypothetical claim which encompassed any of the excipients present in the Teva Atorvastatin Tablets in amounts less than 5% would likely be invalid under 35 U.S.C. § 103 as obvious in view of U.S. Patent No. 5,030,447 ("the '447 patent") which discloses the use of 3.3% magnesium oxide as a stabilizer to prevent the decomposition of a statin, pravastatin, which has the same heptanoic acid side chain as atorvastatin. The scope of equivalents cannot be expanded to encompass the prior art. *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990). Thus, the Teva Atorvastatin Tablets cannot infringe Claim 1 under the doctrine of equivalents for at least these reasons.

Claims 2-3 ultimately depend from Claim 1. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994). Accordingly, the Teva Atorvastatin Tablets cannot infringe any of Claims 2-3, either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 1.

#### 2. Claims 4-6 Are Not Infringed

Claim 4 requires, in part, a pharmaceutical composition comprising "about 5% to about 75% by weight of … calcium carbonate to stabilize the composition."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain the claimed calcium carbonate or an equivalent thereof. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 4, either literally or under the doctrine of equivalents.

Claims 5-6 ultimately depend from Claim 4. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide,* 38 F.3d at 1199. Accordingly, the Teva Atorvastatin Tablets cannot infringe any of Claims 5-6, either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 4.

**3. Claim 7 Is Not Infringed**

Claim 7 requires, in part, a pharmaceutical composition comprising, "an effective amount of calcium carbonate."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain the claimed calcium carbonate or an equivalent thereof. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 7, either literally or under the doctrine of equivalents.

**4. Claim 10 Is Not Infringed**

Claim 10 requires, in part, adding an effective amount of calcium carbonate to the composition of claim 8.

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain the claimed calcium carbonate or an equivalent thereof. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 10, either literally or under the doctrine of equivalents.

**5. Claims 13-15 Are Not Infringed**

Claim 13 requires, in part, "adding an effective amount of calcium carbonate."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain the claimed calcium carbonate or an equivalent thereof. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 13, either literally or under the doctrine of equivalents.

Claims 14-15 ultimately depend from Claim 13. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide,* 38 F.3d at 1199. Accordingly, the Teva Atorvastatin Tablets cannot infringe any of Claims 14-15, either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 13.

### 6. Claim 16 Is Not Infringed

Claim 16 requires, in part, "adding an effective amount of calcium carbonate."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain the claimed calcium carbonate or an equivalent thereof. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 16, either literally or under the doctrine of equivalents.

### 7. Claims 17-19 Are Not Infringed

Claim 17 requires, in part, a pharmaceutical composition comprising "about 5% to about 75% by weight of ... at least one stabilizing pharmaceutically acceptable calcium or lithium salt additive."

The Teva Atorvastatin Tablets do not contain a calcium or lithium salt additive. Accordingly, the Teva Atorvastatin Tablets cannot literally infringe Claim 17.

Moreover, only the filler and disintegrant in the Teva Atorvastatin Tablets are present in amounts which exceed the minimum amount of stabilizer required by Claim 17, *i.e.* 5%, and they are not classified as stabilizers. The remaining excipients are present in amounts which are substantially less than 5% by weight of the tablet. Consequently, even if any of the remaining excipients in the Teva Atorvastatin Tablets functioned as a stabilizer, they could not be an equivalent of "about 5% to about 75%" of stabilizer as required by Claim 17. *Tegal Corp.*, 2002 U.S. App. Lexis 1992.

In addition, Claim 17 of the '971 patent cannot be infringed under the doctrine of equivalents because a hypothetical claim which encompassed any of the excipients present in the Teva Atorvastatin Tablets in amounts less than 5% would be invalid under 35 U.S.C. § 103 over the '447 patent for the reasons discussed in connection with Claim 1. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 17 under the doctrine of equivalents for at least this reason.

Claims 18-19 depend from Claim 17. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide,* 38 F.3d at 1199. Accordingly, the Teva Atorvastatin Tablets cannot infringe any of Claims 18-19, either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 17.

## B. Claims 8-9 And 11-12 Are Invalid

Claims 8-9 and 11-12 are invalid as anticipated under 35 U.S.C. § 102(b) by U.S. Patent No. 4,681,893 ("the '893 patent") to Roth.

### 1. The Scope And Content Of The Prior Art

The '893 patent issued on July 21, 1987 and thus is prior art to the '971 patent under 35 U.S.C. § 102(b). The '893 patent expressly discloses the genus of compounds of claim 8 (which includes atorvastatin). The '893 patent further states that "[f]or preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid." '893 patent, col. 8, ll. 18-20. The '893 patent also identifies alkaline earth metal salts, such as magnesium carbonate, as a suitable carrier. '893 patent, col. 8, l. 41.

### 2. Claim 8 Is Invalid

The '971 patent does not define the term "an effective amount" which appears in Claim 8. However, the '971 patent states that the invention "provides a stable solid oral pharmaceutical composition containing about 5% to about 75% of the stabilizer calcium carbonate by weight of the composition" ('971 patent, col. 3, ll. 61-64), thereby signifying that an amount of stabilizer above 5% would be effective at stabilizing the composition. The '893 patent teaches the preparation of a tablet containing about 5 to 70% active ingredient, thus allowing from about 30 to about 95% of the carrier. Accordingly, formulating a compound of claim 8 with a stabilizing effective amount of an inert pharmaceutically acceptable carrier, e.g. magnesium carbonate, is an inherent result of following the teaching of the '893 patent. Consequently, the '893 patent anticipates Claim 8 under 35 U.S.C. §102(b).

### 3. Claim 9 Is Invalid

Claim 9, dependent from Claim 8, adds the limitation that the alkaline earth metal salt is selected from calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide. Claim 9 is invalid as anticipated for the same reasons set forth above with respect to Claim 8.

### 4. Claim 11 Is Invalid

Claim 11, dependent from Claim 8, adds the limitation that M is a pharmaceutically acceptable alkaline earth metal salt. The '893 patent discloses, for example, magnesium and calcium salts as suitable pharmaceutically acceptable salts. Thus, Claim 11 is also invalid as anticipated for the same reasons set forth above with respect to Claim 8.

### 5. Claim 12 Is Invalid

Claim 12, dependent from Claim 11, adds the limitation that the alkaline earth metal salt is selected from calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide. Claim 12 is invalid as anticipated for the same reasons set forth above with respect to Claim 8.

## VII. TEVA'S ATORVASTATIN TABLETS WILL NOT INFRINGE ANY VALID AND ENFORCEABLE CLAIM OF THE '156 PATENT

The claims of the '156 patent are directed to crystalline Form I atorvastatin hydrate (claims 1-27, 45, 47, 52-55, 61-99, 110-112 and 115), crystalline Form II atorvastatin or a hydrate thereof (claims 28-35, 56-57, 100-105, 113 and 116), and crystalline Form IV atorvastatin or a hydrate thereof (claims 36-44, 46, 48-51, 58-60, 106-109, 114 and 117). The claims recite 2θ values of the peaks in PXRD patterns obtained using $CuK_\alpha$ radiation and/or $^{13}C$ nuclear magnetic resonance chemical shifts for the different forms of atorvastatin. There is no detectable amount of Form I, Form II or Form IV atorvastatin in Teva's atorvastatin active pharmaceutical ingredient ("API") or Teva's Atorvastatin Tablets. Furthermore, Teva's Atorvastatin Tablets and Teva's API do not have the PXRD pattern or $^{13}C$ NMR spectrum of Form I, Form II and Form IV atorvastatin. Accordingly, Teva's Atorvastatin Tablets cannot literally infringe any claim of the '156 patent.

Moreover, the claims of the '156 patent cannot be infringed under the doctrine of equivalents at least because Teva's atorvastatin API and tablets do not include an equivalent to the limitation of Form I, Form II or Form IV atorvastatin, as those terms are used in the '156 patent. The '156 patent distinguishes the crystalline forms by differences in their PXRD and $^{13}C$ NMR spectra. As neither Teva's atorvastatin API nor tablets have the spectra identified for Form I, Form II or Form IV atorvastatin, as set forth in the '156 patent, Teva's Atorvastatin Tablets cannot infringe the '156 patent under the doctrine of equivalents.

## VIII. TEVA'S ATORVASTATIN TABLETS WILL NOT INFRINGE ANY VALID AND ENFORCEABLE CLAIM OF THE '104 PATENT

### A. Claims 1-5 and 7-13 Are Not Infringed

Claim 1 specifies, in part, a pharmaceutical composition comprising a compound of structural formula I and "at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer."

The Teva Atorvastatin Tablets do not contain any surfactants. Accordingly, for at least this reason, the Teva Atorvastatin Tablets cannot literally infringe Claim 1.

Moreover, Claim 1 cannot be infringed under the doctrine of equivalents because the claim element "at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer" is missing in its entirety from the Teva Atorvastatin Tablets. Accordingly, the Teva Atorvastatin Tablets cannot infringe Claim 1 under the doctrine of equivalents for at least this reason.

Claims 2-5 and 7-13 ultimately depend from Claim 1. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide,* 38 F.3d at 1199. Accordingly, the Teva Atorvastatin Tablets cannot infringe any of

Claims 2-5 or 7-13 either literally or under the doctrine of equivalents for at least the reasons discussed with respect to Claim 1.

### B. Claim 6 Is Not Infringed

Claim 6 states, in part, a method for preparing a stable pharmaceutical composition comprising a step of mixing an active ingredient of Claim 1, Claim 2 or Claim 4 with "about 5% to about 75% by weight of a stabilizing pharmaceutically acceptable additive." Only the filler and disintegrant in the Teva Atorvastatin Tablets are present in amounts which exceed the minimum amount of stabilizer required by Claim 6, *i.e.* 5%, and they are not classified as stabilizers. Accordingly, the Teva Atorvastatin Tablets would not literally infringe Claim 6 for at least this reason.

Moreover, the remaining excipients in the Teva Atorvastatin Tablets are present in amounts which are substantially less than 5% by weight of the tablet. Consequently, even if any of the remaining excipients in the Teva Atorvastatin Tablets functioned as a stabilizer, they could not be an equivalent of "about 5% to about 75%" of stabilizer as required by Claim 6. *Tegal Corp.*, 2002 U.S. App. Lexis 1992.

In addition, a hypothetical claim which encompassed any of the excipients present in the Teva Atorvastatin Tablets in amounts less than 5% would likely be invalid under 35 U.S.C. § 103 as obvious in view of U.S. Patent No. 5,030,447 ("the '447 patent") which discloses the use of 3.3% magnesium oxide as a stabilizer to prevent the decomposition of a statin, pravastatin, which has the same heptanoic acid side chain as atorvastatin. The scope of equivalents cannot be expanded to encompass the prior art. *Wilson Sporting Goods Co.,* 904 F.2d at 684. Thus, the Teva Atorvastatin Tablets cannot infringe Claim 6 under the doctrine of equivalents for at least these reasons.

### C. Claim 14 Is Not Infringed

Claim 14 requires, in part, a stabilized solid pharmaceutical composition comprising "at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain any surfactants. Accordingly, the Teva Atorvastatin Tablets cannot infringe Claim 14 either literally or under the doctrine of equivalents.

### D. Claims 15-20 Are Not Infringed

Claim 15 states, in part, a method of preparing a stabilized pharmaceutical composition comprising milling an excess of atorvastatin and "dissolving at least one binder additive in aqueous surfactant solution."

The process for preparing the Teva Atorvastatin Tablets does not involve the use of any aqueous surfactant solution. Accordingly, the Teva Atorvastatin Tablets cannot literally infringe Claim 15 for at least this reason.

Moreover, Claim 15 cannot be infringed under the doctrine of equivalents at least because the claim element "dissolving at least one binder additive in aqueous surfactant solution" is missing in its entirety from Teva's process for preparing the Teva Atorvastatin Tablets.

Claims 16-20 ultimately depend from Claim 15. Dependent claims contain all the limitations of the claims from which they depend. If an accused product or method does not infringe an independent claim, it does not infringe any claim that depends therefrom. *Wolverine World Wide,* 38 F.3d at 1199. Accordingly, the Teva Atorvastatin Tablets cannot infringe any of Claims 16-20, either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 15.

### E. Claims 21-22 Are Not Infringed

Claim 21 requires, in part, a peroral pharmaceutical composition comprising "at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer."

As discussed with respect to Claim 1, the Teva Atorvastatin Tablets do not contain any surfactants. Accordingly, the Teva Atorvastatin Tablets cannot infringe Claim 21 either literally or under the doctrine of equivalents.

Claim 22 depends upon Claim 21. Dependent claims contain all the limitations of the claims from which they depend. Accordingly, the Teva Atorvastatin Tablets cannot infringe Claim 22 either literally or under the doctrine of equivalents, for at least the reasons discussed with respect to Claim 21.[1]

## IX. TEVA'S ATORVASTATIN TABLETS WILL NOT INFRINGE ANY VALID AND ENFORCEABLE CLAIM OF THE '995 PATENT

### A. Claim 10 Is Not Infringed

Claim 10 of the '995 patent is directed to the mixture of atorvastatin heptanoic acid and 1-deoxy-1-(methylamino)-D-glucitol. The Teva Atorvastatin Tablets do not contain 1-deoxy-1-(methylamino)-D-glucitol or an equivalent. Accordingly, the Teva Atorvastatin Tablets cannot infringe Claim 10 either literally or under the doctrine of equivalents for at least this reason.

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[1] In addition, because claim 22 of the '104 patent is directed to a method of treatment, Teva cannot directly infringe this claim because it is our understanding that Teva, as a pharmaceutical company, will not directly treat patients with its atorvastatin calcium tablets. Since there can be no direct infringement of claim 22 there can also be no inducement of infringement.

### B. Claims 1-9 And 11-12 Are Invalid

For the reasons set forth below, Claims 1-9 and 11-12 are invalid (1) as anticipated under 35 U.S.C. § 102(b) by the '893 patent; (2) as obvious under 35 U.S.C. § 103 in view of the '893 patent in combination with prior art knowledge that the R-trans enantiomer (lactone form) or the [R-(R*,R*)] enantiomer (opened acid or salt form) of other statins was active as an inhibitor of HMG-CoA reductase and that a person of ordinary skill in the art would have been familiar with methods for separating racemic mixtures of statins into their individual enantiomers, as exemplified in U.S. Patent No. 4,375,475 ("the '475 patent"); (3) for failure to comply with 35 U.S.C. § 112, ¶ 4; (4) under the doctrine of obviousness type double patenting over U.S. Patent No. 5,003,080 ("the '080 patent") which claims a process of preparing (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone); and/or (5) under the doctrine of obviousness type double patenting over U.S. Patent No. 5,216,174 ("the '174 patent") which claims a process of preparing a compound of Formula XII.

#### 1. The Decisions of The District Court And The Federal Circuit

In *Pfizer, Inc. v. Ranbaxy Labs., Ltd.*, 457 F.3d 1284, the Federal Circuit held that Claim 6 of the '995 patent was invalid under 35 U.S.C. § 112. In addition, the Federal Circuit affirmed the lower court's construction of Claim 1 of the '893 patent and stated that "the district court correctly found that no intrinsic evidence limits claim 1 of the '893 patent to trans-racemates, as opposed to an R-trans enantiomer, S-trans enantiomer or any (equal or unequal) mixtures thereof." *Id.* at 1289.

#### 2. Claim 1 Is Invalid

Claim 1 of the '995 patent claims specific enantiomers, *i.e.*, atorvastatin lactone, atorvastatin acid and pharmaceutically acceptable salts thereof. The '893 patent sets forth the structure of atorvastatin lactone as Compound 1 of Table 1 (See Table 1 in Columns 7-8 of the '893 patent). Thus, the '893 patent anticipates Claim 1 of the '995 patent.

Even if the court finds that Compound 1 of Table 1 in the prior art '893 patent discloses only a racemic mixture, the prior art taught that the R-trans enantiomer (lactone form) or the [R-(R*,R*)] enantiomer (opened acid or salt form) of other statins was active as an inhibitor of HMG-CoA reductase. In addition, as of the filing date of the '893 patent, May 30, 1986, a person of ordinary skill in the art would have been familiar with methods for separating racemic mixtures of statins into their individual enantiomers, as exemplified in U.S. Patent No. 4,375,475. Furthermore, in *Aventis v. Lupin*, 499 F.3d 1293, the Federal Circuit stated that "a purified compound is not always prima facie obvious over the mixture....However, if it is known that some desirable property of a mixture derives in whole or in part from a particular one of its components, or if the prior art would provide a person of ordinary skill in the art with reason to believe that it is so, the purified compound is prima facie obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified." *Id.* at 1301. Accordingly, the '893 patent would render Claim 1 obvious.

There are no unexpected results to negate a finding of obviousness. The experimental data taken as a whole, do not support the assertion, made by the patentees during prosecution of the '995 patent, that the R-trans enantiomer (lactone form) or the [R-(R*,R*)] enantiomer (open acid or salt form) was ten-fold more active than the racemic mixture *in vitro*. Rather, the data show that the R-trans enantiomer (lactone form) or the [R-(R*,R*)] enantiomer (open acid or salt form) was approximately twice as active, a result that is neither surprising nor unexpected (a finding noted by the Federal Court of Australia in a decision involving the Australian counterpart to the '995 patent. *Ranbaxy Australia Pty. Ltd. v. Warner Lambert Co. LLC* (Dec. 20, 2006)).

Furthermore, there is no basis for attributing the business success of LIPITOR® to the claims of the '995 patent and thus there is no "nexus" to the '995 patent.

In addition, Claim 14 of the '080 patent claims a process of preparing atorvastatin lactone. Because Claim 1 of the '995 patent claims, *inter alia*, atorvastatin lactone, Claim 14 of the '080 patent would render Claim 1 invalid for obviousness-type double patenting.

In addition, Claim 7 of the '174 patent claims a process of preparing a compound of Formula XII (Formula XII depicts the compound atorvastatin acid). A person of ordinary skill in the art would have been familiar with methods for separating racemic mixtures of statins into their individual enantiomers, as exemplified in U.S. Patent No. 4,375,475. Because Claim 1 of the '995 patent claims, *inter alia*, atorvastatin acid, Claim 7 of the '174 patent would render Claim 1 invalid for obviousness-type double patenting.

### 3. Claims 2 And 3 Are Invalid

Claims 2 and 3 of the '995 patent claim atorvastatin acid and atorvastatin lactone, respectively. As discussed above, the '893 patent discloses atorvastatin lactone. The '893 patent also discloses "hydroxy acids…derived from the opening of the lactone ring of the compounds of structural formula I above." '893 patent, col. 2, ll. 40-43. Thus, the '893 patent anticipates Claims 2 and 3 of the '995 patent.

In addition, Claims 2 and 3 would also be invalid as obvious for the reasons set forth above in connection with Claim 1.

Claim 3 would also be invalid for obviousness-type double patenting for the reasons set forth above in connection with Claim 1.

Furthermore, Claim 14 of the '080 patent claims a process of making atorvastatin lactone. The '893 patent discloses at least racemic mixtures, including the racemic form of atorvastatin lactone and the racemic form of atorvastatin (i.e. atorvastatin acid). *See* '995 Reissue, October 15, 2007, Amendment in Response to First Reissue Office Action at 17. Thus, based on the disclosure of the '893 patent, one of skill in the art would have known to open the lactone ring of atorvastatin lactone, formed by the process of claim 14 of the '080 patent, to obtain atorvastatin acid. Thus, Claim 14 of the '080 patent in combination with the disclosure of the '893 patent would render Claim 2 of the '995 patent invalid for obviousness-type double patenting.

Alternatively, Claim 7 of the '174 patent would render Claim 2 invalid for obviousness-type double patenting for the reasons set forth above in connection with Claim 1.

### 4. Claims 4-5 And 7-9 Are Invalid

Claims 4-5 and 7-9 of the '995 patent depend directly from Claim 2 and are directed to the monosodium, monopotassium, N-methylglucamine, hemimagnesium and hemizinc salts of atorvastatin, respectively.

Claim 2, which depends from Claim 1, is directed to atorvastatin heptanoic acid and does not include any recitation of "pharmaceutically acceptable salts thereof." As the Federal Circuit found with respect to Claim 6, Claims 4-5 and 7-9 "fail[] to 'specify a further limitation of the subject matter' of the claim to which [they refer] because [they are] completely outside the scope of claim 2." *Pfizer*, 457 F.3d at 1292. Accordingly, Claims 4-5 and 7-9 are invalid for failure to comply with 35 U.S.C. § 112, ¶ 4.

### 5. Claim 6 Is Invalid

Claim 6 was held invalid by the Federal Circuit under 35 U.S.C. § 112, ¶ 4 for failure to specify a further limitation to the claim from which it depends. See *Pfizer*, 457 F.3d at 1291.

### 6. Claims 11 And 12 Are Invalid

Claims 11 and 12 are directed to a pharmaceutical composition comprising a hypocholesterolemic effective amount of a compound of Claim 1 and a method of inhibiting cholesterol synthesis comprising administering a compound of Claim 1 in a unit dosage form, respectively. The '893 patent discloses that "[t]he compounds of this invention are useful as hypocholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol through inhibition of the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase)." '893 patent, col. 7, ll. 32-37. Thus, the '893 patent would anticipate Claims 11 and 12 of the '995 patent. *See also Aventis v. Lupin,* 499 F.3d at 1303.

Furthermore, for the reasons set forth above in connection with Claim 1, Claims 11 and 12 would be invalid as obvious under 35 U.S.C. § 103 in view of the disclosure of the '893 patent.

In addition, Claim 14 of the '080 patent, in view of the '893 patent, would render Claims 11 and 12 of the '995 patent invalid for obviousness-type double patenting.

Alternatively, Claim 7 of the '174 patent, in view of the '893 patent, would render Claims 11 and 12 invalid for obviousness-type double patenting for the reasons set forth above.

## X. CONCLUSION

For at least the foregoing reasons, the manufacture, use, sale, or offer for sale in the United States, and/or importation into the United States, of Teva's Atorvastatin Tablets will not infringe any valid or enforceable claim of the '971, '156, '104 or '995 patents. Teva USA reserves the right to assert additional grounds, reasons or authorities that any or all of the claims of the '971, '156, '104 or '995 patents are invalid, unenforceable, or not infringed.

**ABBREVIATED NEW DRUG APPLICATION 78-773**
**OFFER OF CONFIDENTIAL ACCESS**
**PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)**

**WHEREAS** Teva Pharmaceuticals USA, Inc. ("Teva USA") has provided notice to Pfizer, Inc. and Warner-Lambert Company (hereinafter "Recipients") that Teva USA submitted to the U.S. Food and Drug Administration ("FDA") an amendment to Abbreviated New Drug Application 78-773 for Teva USA's Atorvastatin Calcium Tablets, Eq. 10 mg Base, Eq. 20 mg Base and Eq. 40 mg Base (hereinafter referred to in whole or in part as the "ANDA"), containing a Paragraph IV certification with respect to U.S. Patent Nos. 6,126,971, 5,969,156, 5,686,104 and 5,273,995 (the "Listed Patents") which are listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations"; and

**WHEREAS** this document constitutes Teva USA's Offer of Confidential Access to relevant portions of that ANDA pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement;
>
> and

**WHEREAS** Teva USA offers to provide Recipients confidential access to the relevant portions of the ANDA subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA; and

**WHEREAS** this document accompanies Teva USA's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Listed Patents;

**NOW, THEREFORE**, Teva USA makes this offer:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions recited in clause 2 below, Teva USA hereby provides Recipients this Offer of Confidential Access for the sole purpose of determining whether to bring an action referred to in 21 U.S.C. § 355(j)(5)(B)(iii) with respect to any of the Listed Patents.

2. The right of confidential access offered herein is subject to the following restrictions as to persons entitled to access, and the use and disposition of any information accessed, pursuant to this Offer of Confidential Access:

**A.** **Persons Entitled to Access**: Persons entitled to access (hereinafter referred to as "Authorized Evaluators") under this Offer of Confidential Access are restricted to outside counsel engaged by Recipients to represent Recipients and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that:

(1) Such outside counsel has been identified to Teva USA in writing;

(2) Within 5 business days of receiving such written identification, Teva USA has not objected, in writing, to provision of confidential access to the identified outside counsel.

**B.** **Materials Accessible by Authorized Evaluators**: A copy of the ANDA, redacted to remove portions of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

**C.** **Use of the ANDA and Information in the ANDA**:

(1) Subject to paragraph 2(D)(2)(a), use of the ANDA, and all information contained therein or derived therefrom, and all notes, analyses, studies, or documents prepared by Authorized Evaluators to the extent they reflect information contained in or derived from the ANDA furnished herein, is for the sole and limited purpose of evaluating possible infringement of any of the Listed Patents and for no other purpose.

(2) Authorized Evaluators shall not disclose any information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any information contained in or derived from the ANDA, to any person other than an Authorized Evaluator.

(3) Notwithstanding the provisions of subparagraphs 2(C)(1) and 2(C)(2) above, Authorized Evaluators shall be permitted to advise Recipients on whether or not to assert any of the Listed Patents, provided, however, that the information contained in or derived from the ANDA is not thereby disclosed.

**D.** **Disposition of the Information in the ANDA:**

(1) If Recipients do not assert any of the Listed Patents against Teva USA within 45 days of receipt of the Notice and Detailed Statement (the "45-day period") which this offer accompanies, Authorized Evaluators

shall, and Recipients shall direct and ensure that Authorized Evaluators, within 30 days after the expiration of the 45-day period, destroy or send to Teva USA the portions of the ANDA provided, and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information contained in or derived from the ANDA, and Recipients or Authorized Evaluators shall notify Teva USA that this has been done.

(2) Recipients agree that if any Recipient asserts any of the Listed Patents against Teva USA within 45 days of receipt of the Notice and Detailed Statement which this offer accompanies:

(a) While the litigation is pending, the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information contained in or derived from the ANDA, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Teva USA. Until such a protective order is entered, subsection 2(C)(2) above continues to apply.

(b) Recipients shall direct and ensure that Authorized Evaluators destroy the portions of the ANDA provided and all notes, analyses, studies or other documents prepared or received by Authorized Evaluators to the extent that they reflect information contained in or derived from the ANDA, within thirty (30) days after the final determination of the action brought against Teva USA.

(3) Notwithstanding the provisions of subparagraphs 2(D)(1) and 2(D)(2) above, the Authorized Evaluators identified in subparagraph 2(A) shall be permitted to retain one copy of the portions of the ANDA provided and each note, analysis, study or other document prepared by Authorized Evaluators to the extent that they reflect information in the ANDA.

**E.** **Accidental Disclosure**: Should information contained in or derived from the ANDA be disclosed, inadvertently or otherwise, Recipients shall, at Recipients' earliest opportunity, contact Teva USA and identify:

(1) What has been disclosed;

(2) The individuals to whom such information has been disclosed; and

(3) Steps taken by Recipients and Authorized Evaluators to ensure the information contained in or derived from the ANDA continues to be treated pursuant to the terms of this agreement and is not further disseminated.

3. Recipients and Authorized Evaluators recognize that violation of any provision of this Offer of Confidential Access will cause irreparable injury to Teva USA, and that an adequate legal remedy does not exist. Teva USA, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Recipients and Authorized Evaluators from violating the terms of this Offer of Confidential Access. It is further agreed that in such an action Teva USA is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer of Confidential Access be found by a court of competent jurisdiction to be illegal, unconstitutional and/or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use information contained in or derived from the ANDA, except for the purpose expressly stated herein.

6. This Agreement shall be governed by the laws of the State of New York, without giving effect to its conflicts of law or choice of law principles.

7. Each of Recipients, Authorized Evaluators and Teva USA, irrevocably submit to and accept, generally and unconditionally, the exclusive personal jurisdiction of the courts of the State of New York, and of the U.S. District Court for the Southern District of New York, waives its right to assert any objection or defense based on venue or forum non conveniens and agrees to be bound by any judgment rendered thereby arising under or in respect of this Agreement.

8. When accepted by the parties hereto, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

9. An Authorized Evaluator may request access to the ANDA by executing one copy of this Confidential Access Agreement where indicated and returning the executed copy to Paul H. Fackler within the 45-day period. Thereupon, the terms contained in this document shall be considered an enforceable contract between Teva USA and the Recipients.

TEVA Pharmaceuticals USA, Inc.
By its authorized agent:

Paul H. Fackler, Ph.D.
Vice President, Global Generic Research & Development Biopharmaceutics
TEVA Pharmaceuticals USA, Inc.

Date: March 12, 2008

Recipients
By their authorized agent(s):

Signature: _____

Name (Print): _____

Title: _____

Company: _____

Date: _____

JS 44 (Rev. 11/04)

# CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

**I. (a) PLAINTIFFS**
PFIZER INC, PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT, LTD.

**(b)** County Of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

**(c)** ATTORNEYS (FIRM NAME, ADDRESS AND TELEPHONE NUMBER)
Rudolf E. Hutz (#484)
CONNOLLY BOVE LODGE & HUTZ LLP
1007 N. Orange Street, P.O. Box 2207
Wilmington, Delaware 19899 Telephone: (302) 658-9141

**DEFENDANTS**
TEVA PHARMACEUTICALS USA, INC.,
County Of Residence Of First Listed Defendant: _____
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

ATTORNEYS (IF KNOWN)

**II. BASIS OF JURISDICTION** (Place an "X" In One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

**III. CITIZENSHIP OF PRINCIPAL PARTIES** (Place an "X" In One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

| | PTF | DEF | | PTF | DEF |
|---|---|---|---|---|---|
| Citizen of This State | ☒ 1 | ☐ 1 | **Incorporated *or* Principal Place of Business in This State** | ☐ 4 | ☒ 4 |
| Citizen of Another State | ☐ 2 | ☐ 2 | Incorporated *and* Principal Place of Business in Another State | ☐ 5 | ☐ 5 |
| Citizen or Subject of a Foreign Country | ☐ 3 | ☐ 3 | Foreign Nation | ☐ 6 | ☐ 6 |

**IV. NATURE OF SUIT** (Place an "X" In One Box Only)

**CONTRACT**
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

**REAL PROPERTY**
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

**TORTS**

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

**CIVIL RIGHTS**
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities – Employment
- ☐ 446 Amer. w/Disabilities – Other
- ☐ 440 Other Civil Rights

**PRISONER PETITIONS**
- ☐ 510 Motions to Vacate Sentence

HABEAS CORPUS:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

**FORFEITURE/PENALTY**
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

**LABOR**
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt Relations
- ☐ 730 Labor/Mgmt Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

**BANKRUPTCY**
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

**PROPERTY RIGHTS**
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

**SOCIAL SECURITY**
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

**FEDERAL TAX SUITS**
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS - Third Party 26 USC 7609

**OTHER STATUTES**
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced an Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/ Commodities Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900 Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

**V. ORIGIN** (PLACE AN "X" IN ONE BOX ONLY)

☒ 1 Original Proceeding | ☐ 2 Removed from State Court | ☐ 3 Remanded from Appellate Court | ☐ 4 Reinstated or Reopened | ☐ 5 Transferred from another district (specify) | ☐ 6 Multidistrict Litigation | ☐ 7 Appeal to District Judge from Magistrate Judgment

**VI. CAUSE OF ACTION**
Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity):**
**35 U.S.C. § 271**
Brief description of cause:
**Patent infringement.**

**VII. REQUESTED IN COMPLAINT:** ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 **DEMAND:**
CHECK YES only if demanded in complaint:
**JURY DEMAND:** ☐ YES ☒ NO

**VIII. RELATED CASE(S) IF ANY** (See instructions): JUDGE DOCKET NUMBER
**Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 03-209-JJF; Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 07-138-JJF;**
**Pfizer Inc. et al. v. Teva Pharmaceuticals. Inc., Civil Action No. 07-360-JJF; Pfizer Inc. et al. v. Cobalt Pharmaceuticals, Inc., Civil Action No. 07-790-JJF;**
**Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 08-162-JJF; Pfizer Inc. et al. v. Ranbaxy, Farnan, J., Civil Action No. 08-164-JJF.**

DATE SIGNATURE OF ATTORNEY OF RECORD

**3/24/2008 /s/Rudolf E. Hutz (#484)**

FOR OFFICE USE ONLY

RECEIPT # AMOUNT APPLYING IFP JUDGE MAG. JUDGE

# INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS–44

Authority For Civil Cover Sheet

The JS–44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

**I. (a) Plaintiffs – Defendants.** Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

**II. Jurisdiction.** The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below: federal question actions take precedence over diversity cases.)

**III. Residence (citizenship) of Principal Parties.** This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

**IV. Nature of Suit.** Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

**V. Origin.** Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C. Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

**VI. Cause of Action.** Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statues unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service.

**VII. Requested in Complaint.** Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

**VIII. Related Cases.** This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

**Date and Attorney Signature.** Date and sign the civil cover sheet.